
In The Name Of God

دانشگاه علوم پزشکی قزوین

Liposome & Nanoliposome

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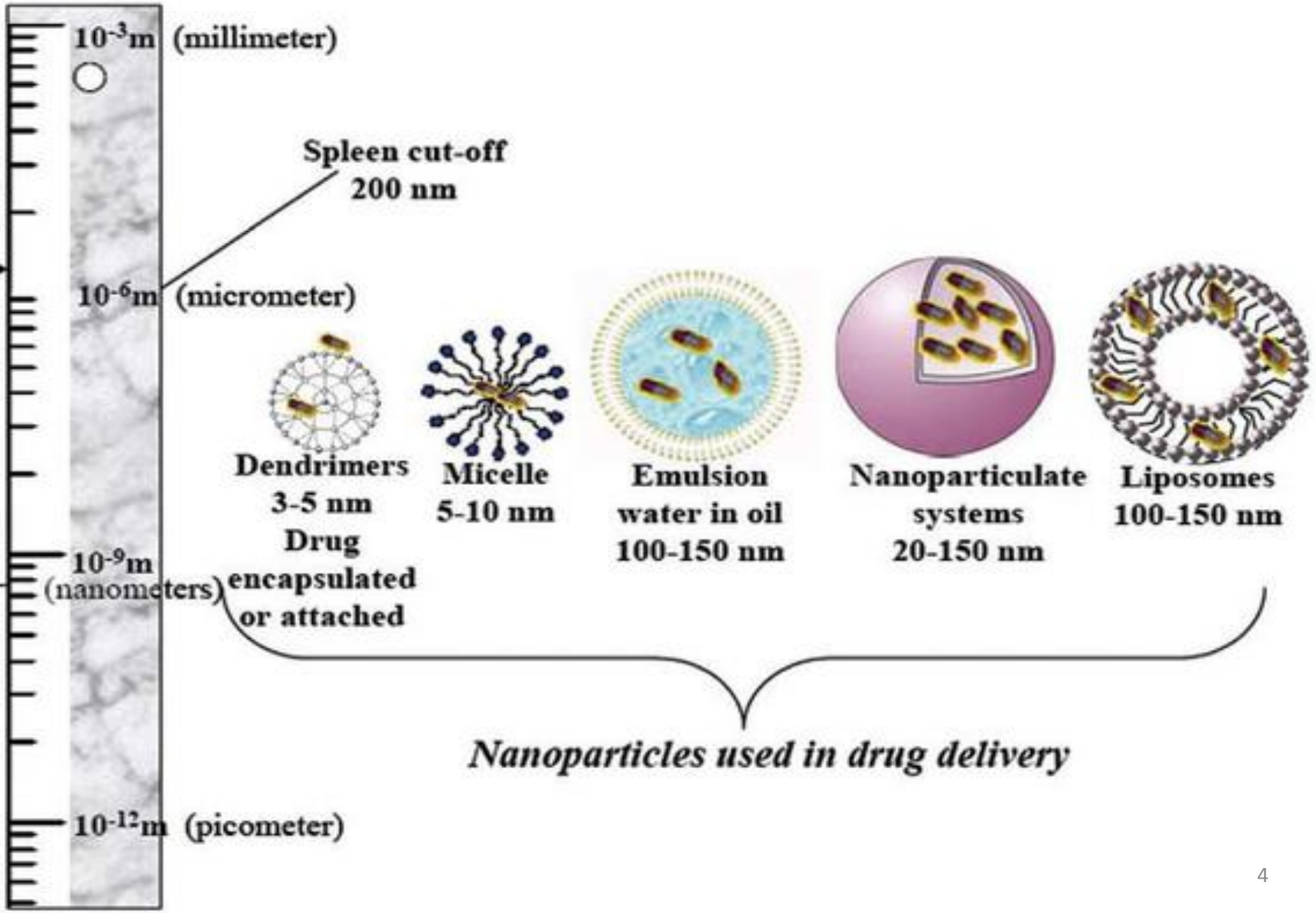
- Statistical Data (Type Of Carriers)
- Introduction
- Classification
- Applications
- Advantages & Disadvantages

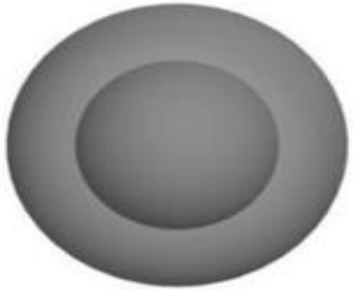
NP systems for drug delivery applications. (Adapted with permission from 119 © 2005 Elsevier; and from 120 © 2005 PharmaVentures Ltd.)



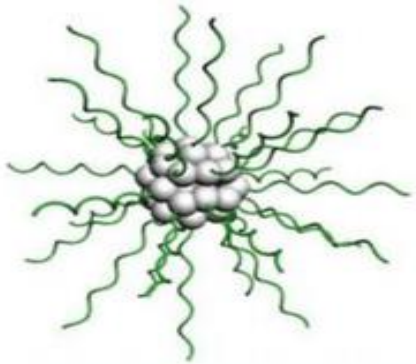
Nanostructures

	A	B	C	D	E	F	G	H	I	J
1		2000-2002	2002-2004	2004-2006	2006-2008	2008-2010	2010-2012	2012-2014	2014-2016	2016-2018
2	liposome	21,900	25,800	26,800	25,500	26,100	27,300	25,300	22,600	19,300
3	nano liposome	110	199	320	591	954	1,550	2,090	2,800	3,380
4	Polymeric micelles	17,300	18,100	18,500	18,200	17,900	15,900	15,600	15,200	16,900
5	Microspheres	28,400	35,200	44,100	50,100	57,200	70,900	74,000	58,500	26,200
6	Nanostructures	30,300	65,400	78,600	165,000	231,000	256,00	302,000	195,000	75,100
7	Nanofibers	3,140	6,800	13,000	17,900	24,700	32,000	47,200	50,200	25,800
8	Protein-DNA complexes	14,200	15,900	17,000	17,300	17,400	17,600	17,000	17,500	16,700
9	Protein-drug conjugates	649	1,060	1,430	1,870	2,340	3,020	3,800	4,320	4,060
10	Dendrimers	7,940	11,000	14,300	17,300	20,300	21,200	21,600	18,700	16,500

https://scholar.google.com/

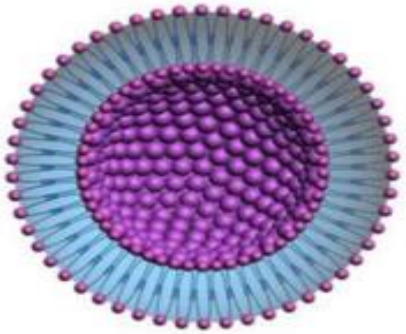


Polymeric Carrier

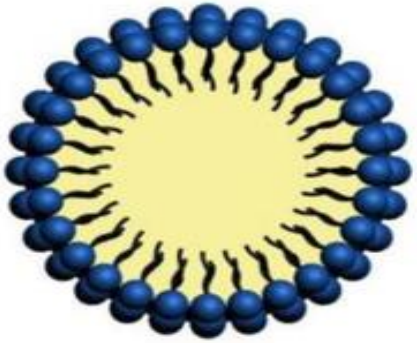


Polymeric Micelle

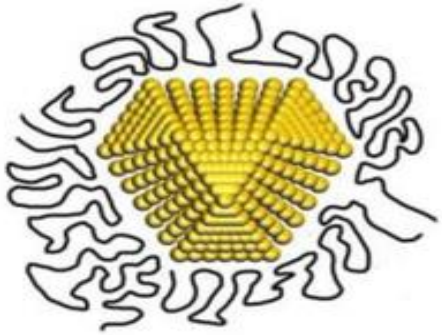
Dendrimer



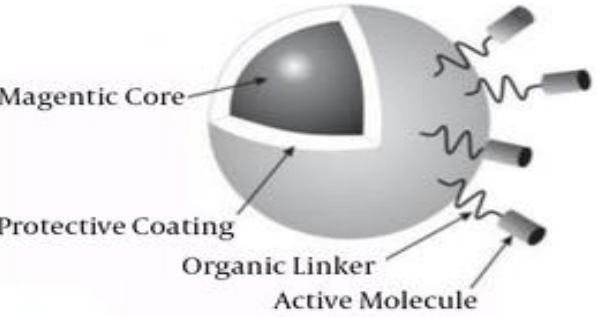
Liposome



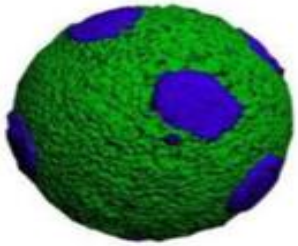
Solid Lipid Carrier



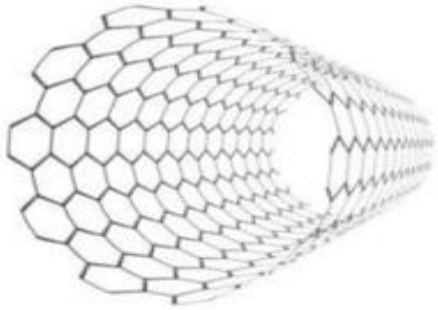
Gold Carrier



Magentic Carrier

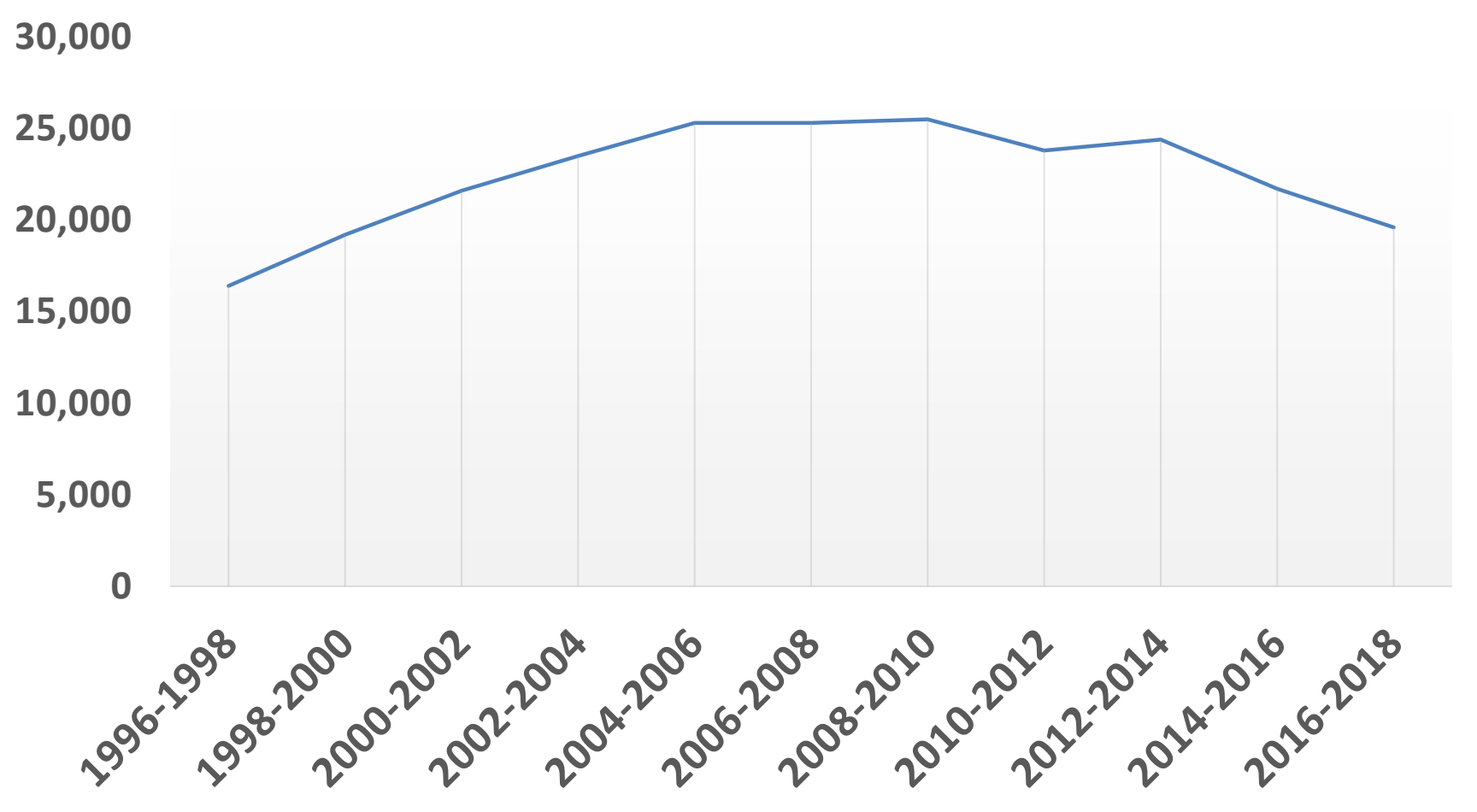


Viral Carrier



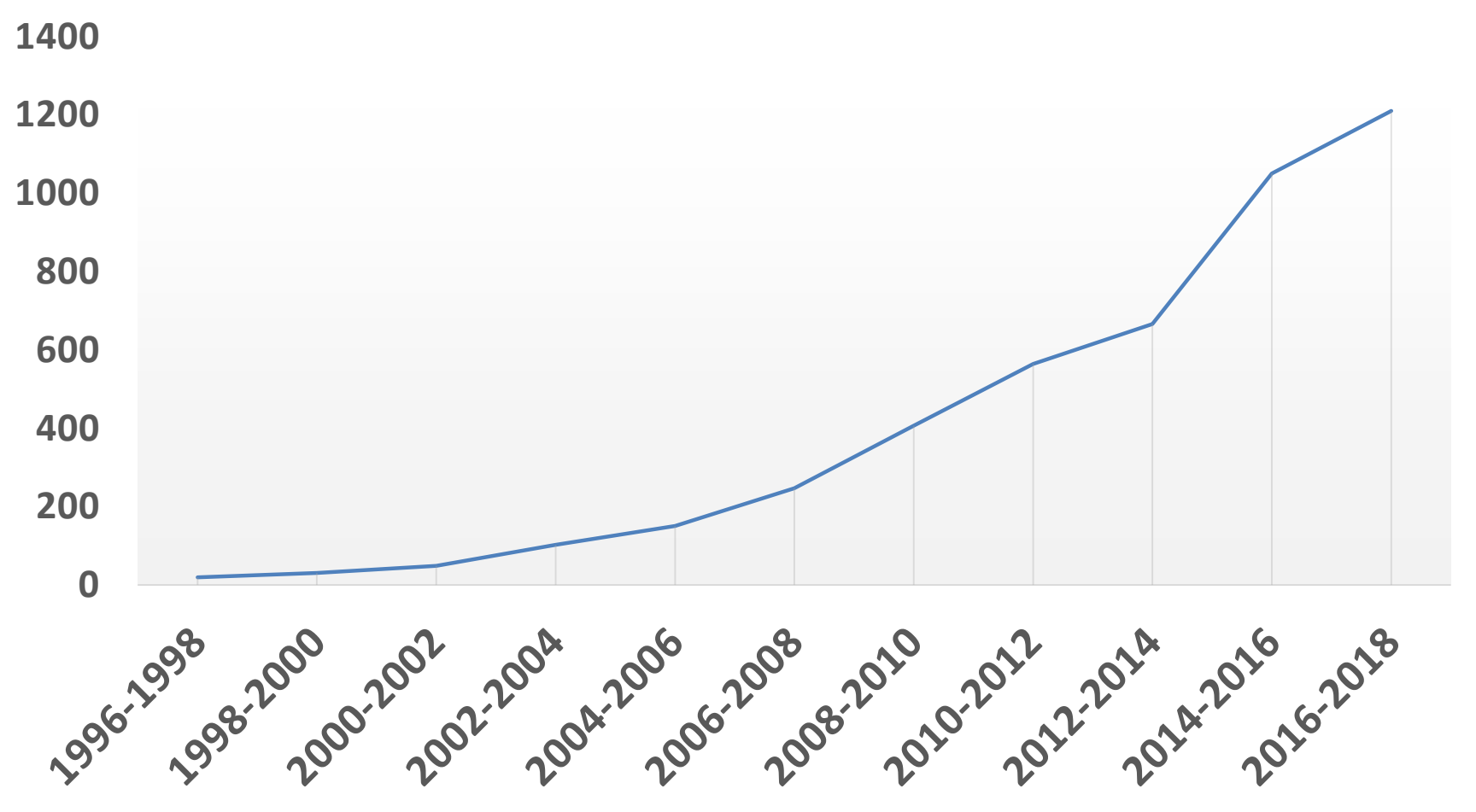
Carbon Carrier

Research Of Liposome Trend



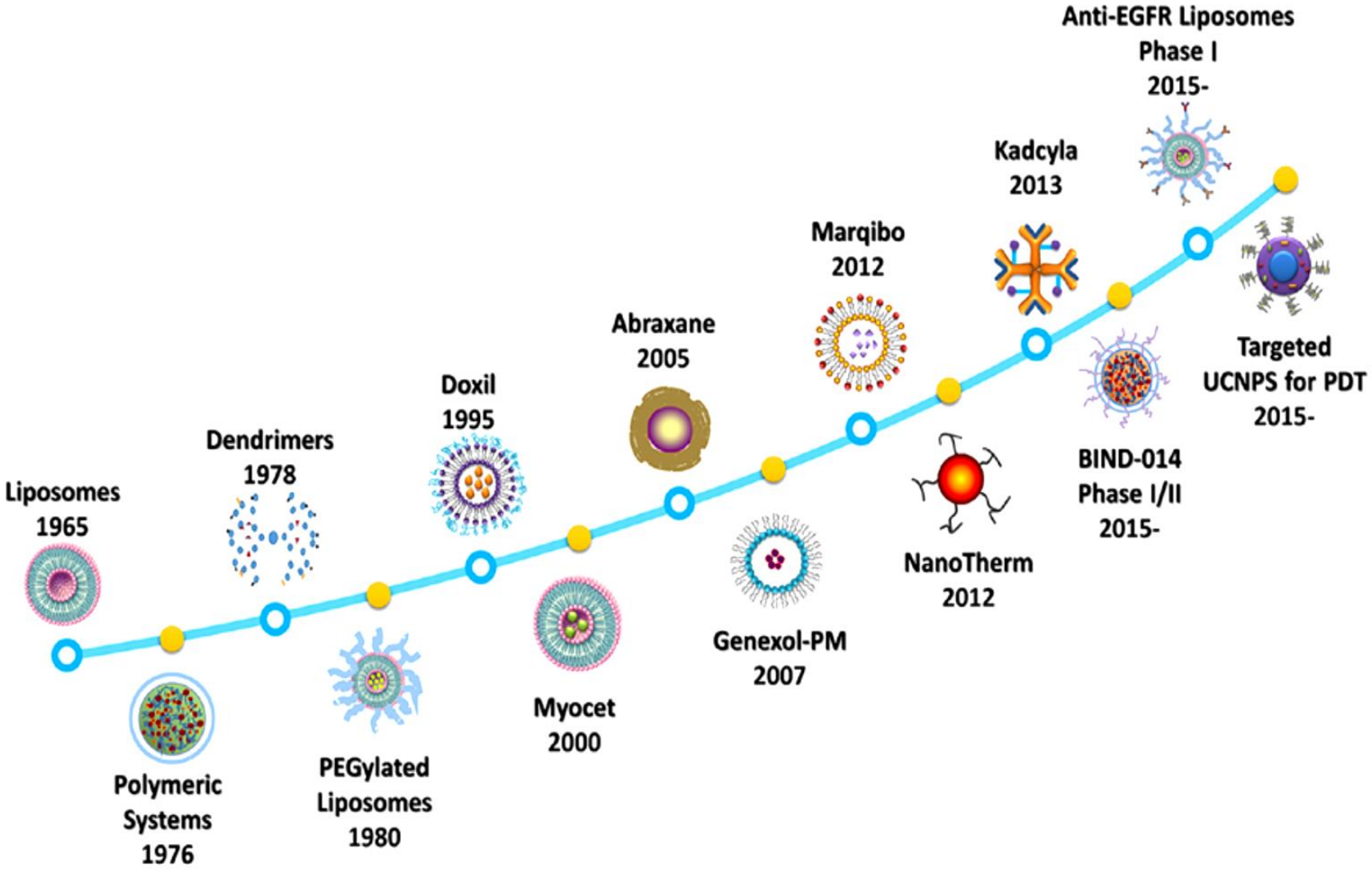
https://scholar.google.com/liposome

Research Of NanoLiposome Trend

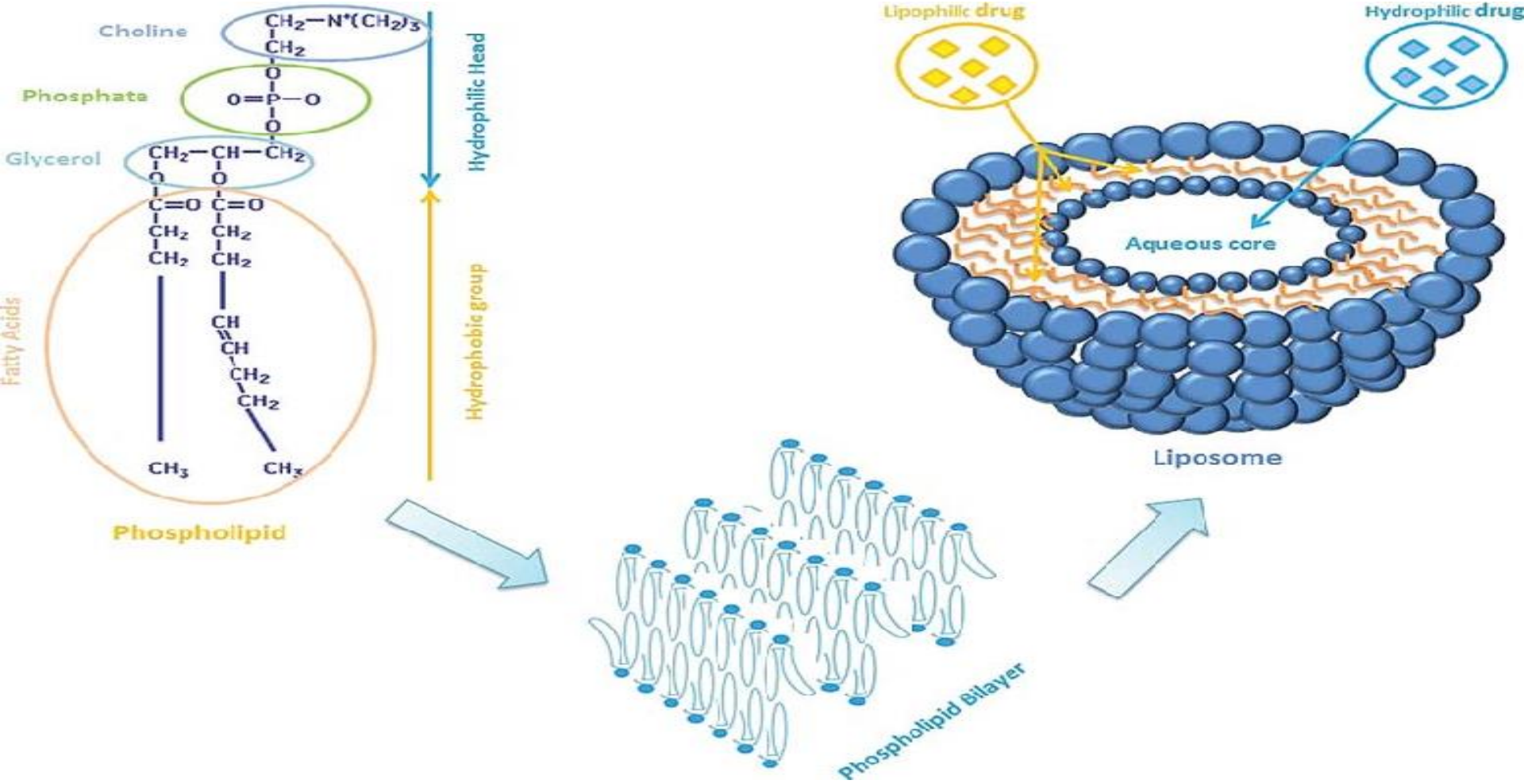


https://scholar.google.com/nanoliposome

Timeline of the development of nanomedicines(15)



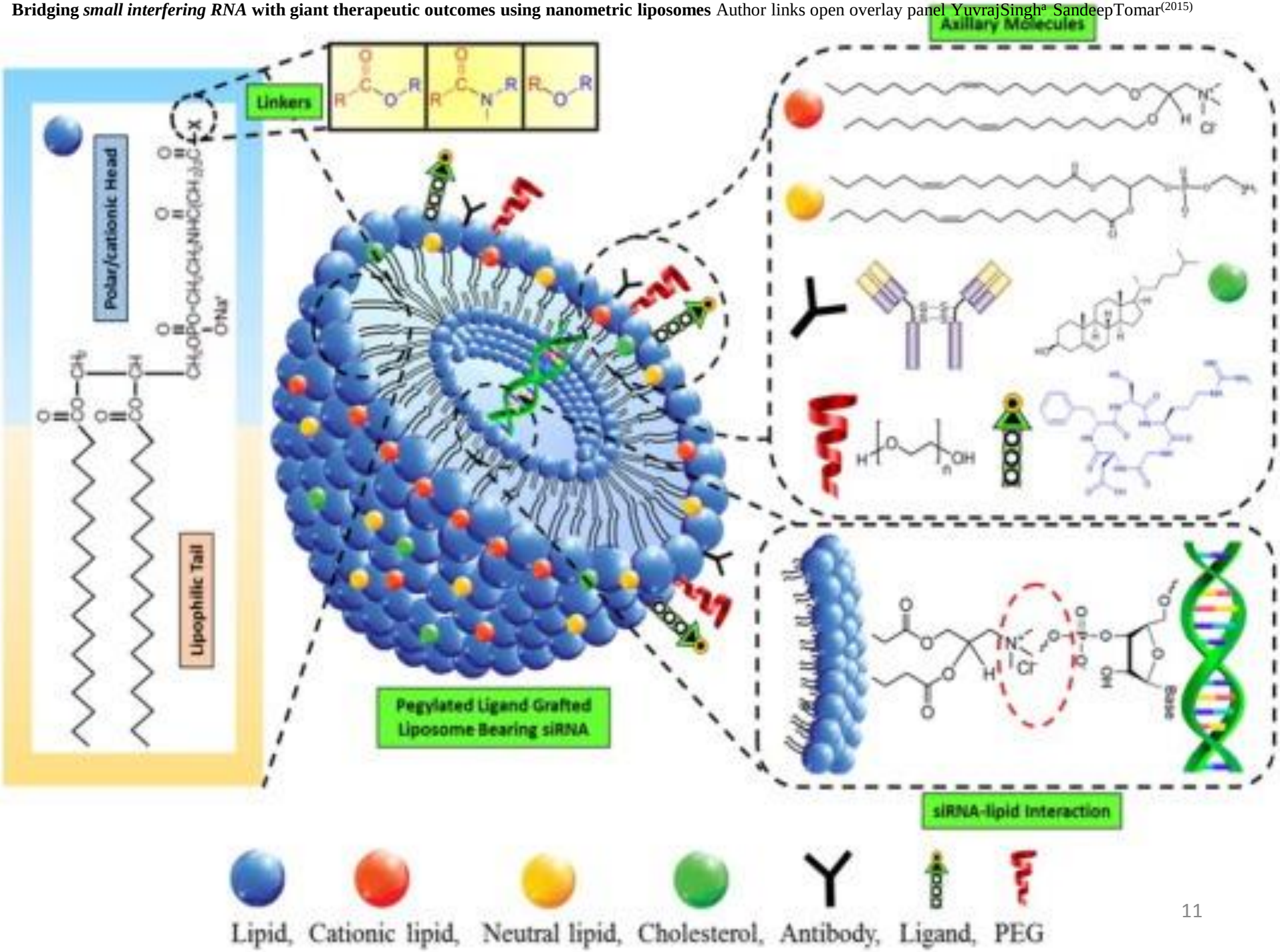
Introduction



https://www.researchgate.net/profile/Abdallah_Laouini

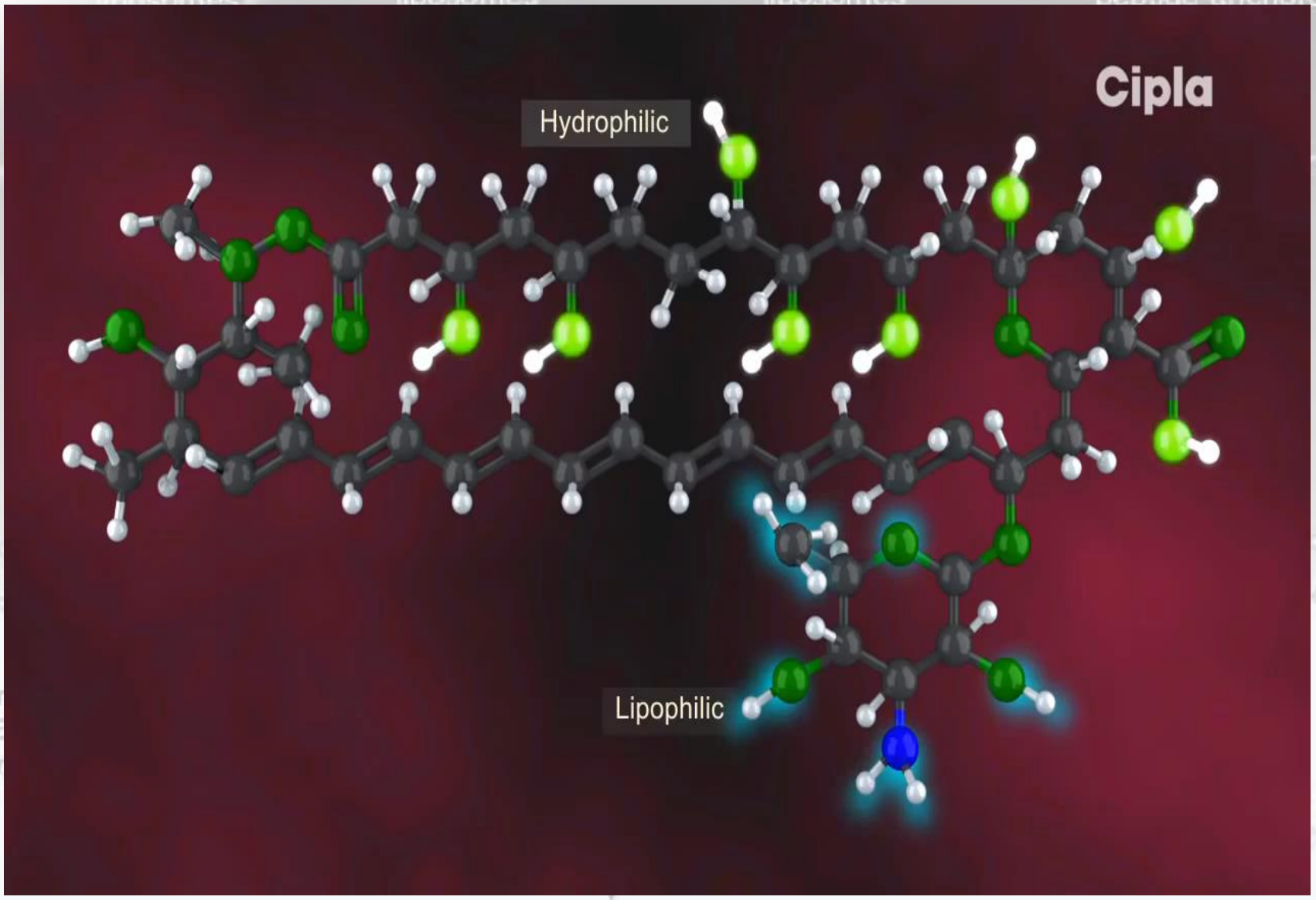
Liposomes were first described by British haematologist Alec D Bangham in 1961 , at the Babraham Institute, in Cambridge.[1]

Bridging *small interfering RNA* with giant therapeutic outcomes using nanometric liposomes Author links open overlay panel YuvrajSingh[a] SandeepTomar[(2015)]



Liposome's formation

https://www.youtube.com/results?search_query=Liposome_+A+Technological+Marvel+Module2.avi



https://www.youtube.com/results?search_query=Liposome_+A+Technological+Marvel+Module2.avi

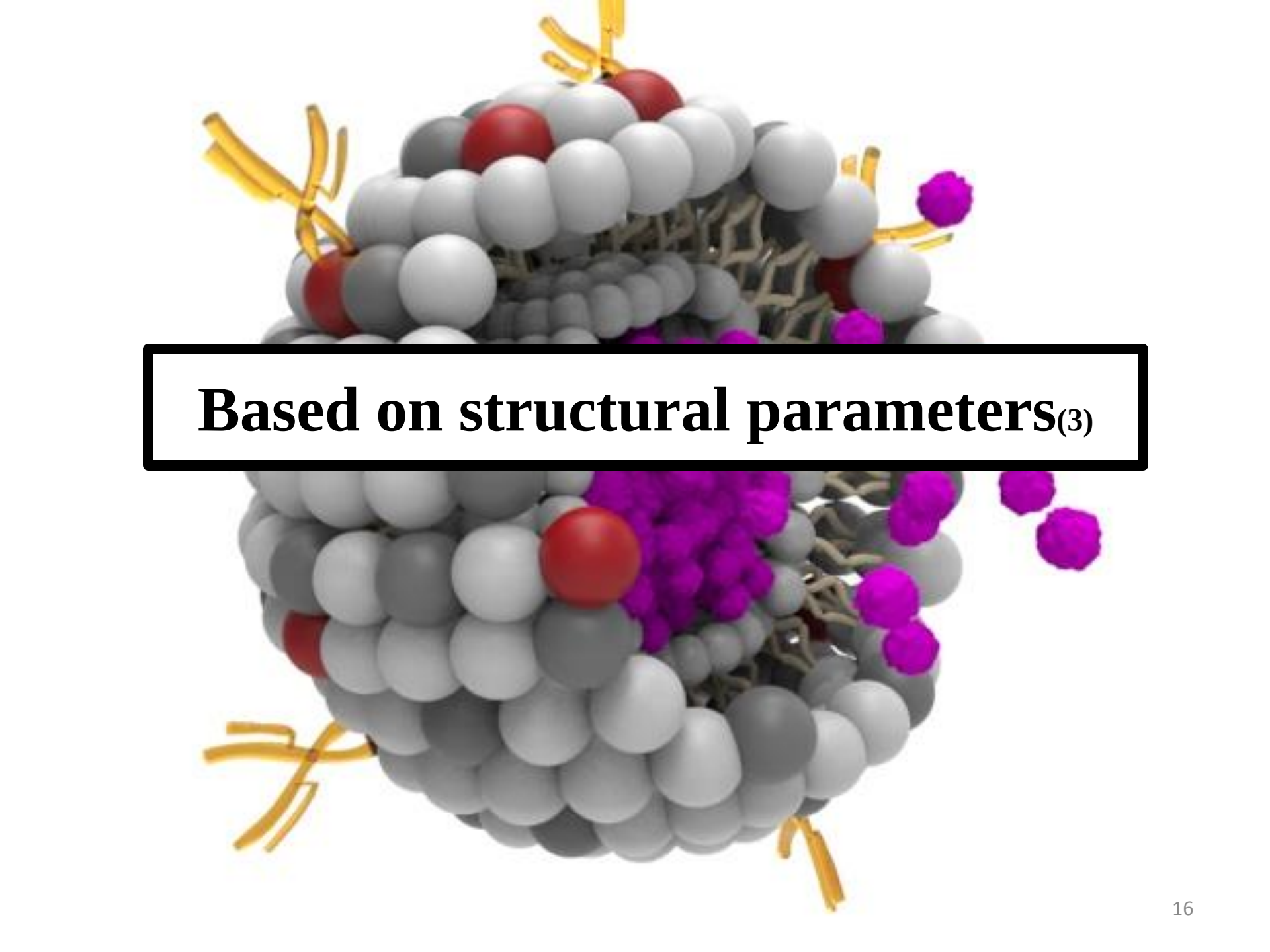
Why do we use of liposomes?(1)

- ✓ Manufactured **size** controlled
- ✓ **High** drug/lipid ratios
- ✓ **Long**-circulating (stealth coating)
- ✓ **Mimic** the properties of biological membranes[28]
- ✓ Target-**specific** delivery
- ✓ Enhanced intracellular **penetration**
- ✓ Contrast enhancement for **image-guided** therapy

Classification(3)

Based on :

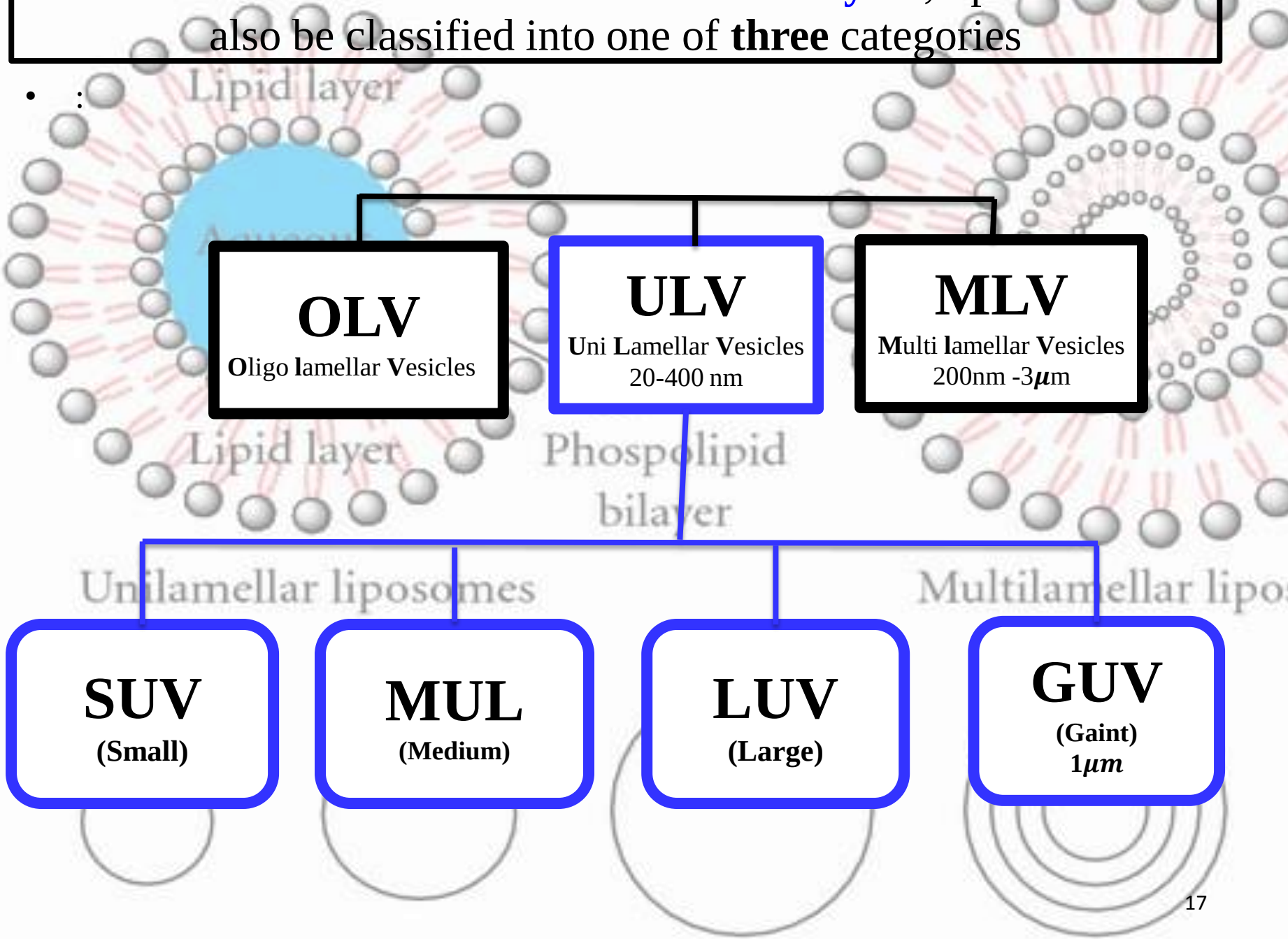
- **structural** parameters
- method of **preparation**
- **composition** and **applications**



Based on structural parameters(3)

On the basis of their **size** and **number of bilayers**, liposomes can also be classified into one of **three** categories

- :



OLV
Oligo **l**amellar **V**esicles

ULV
Uni **L**amellar **V**esicles
20-400 nm

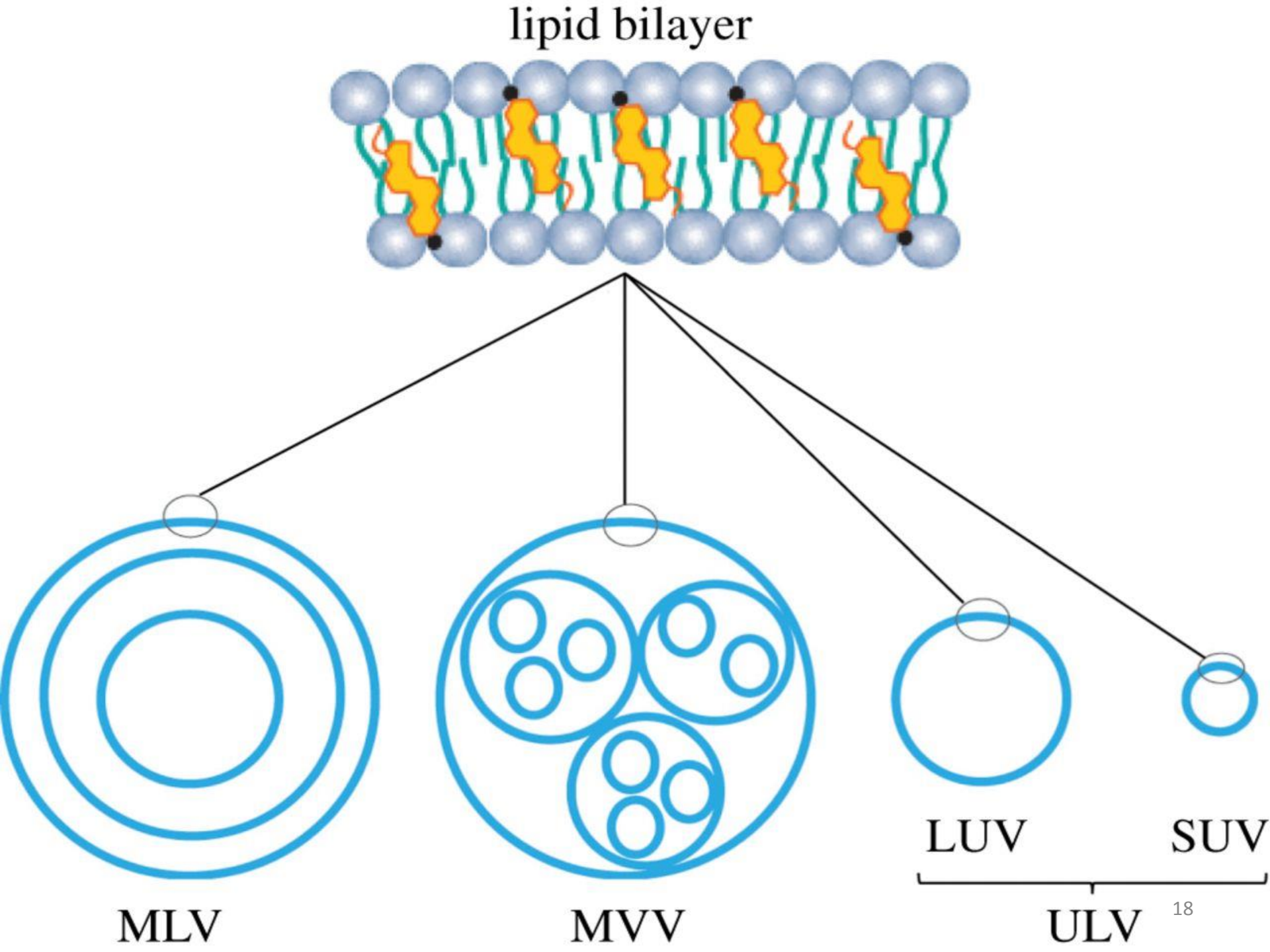
MLV
Multi **l**amellar **V**esicles
200nm -3μm

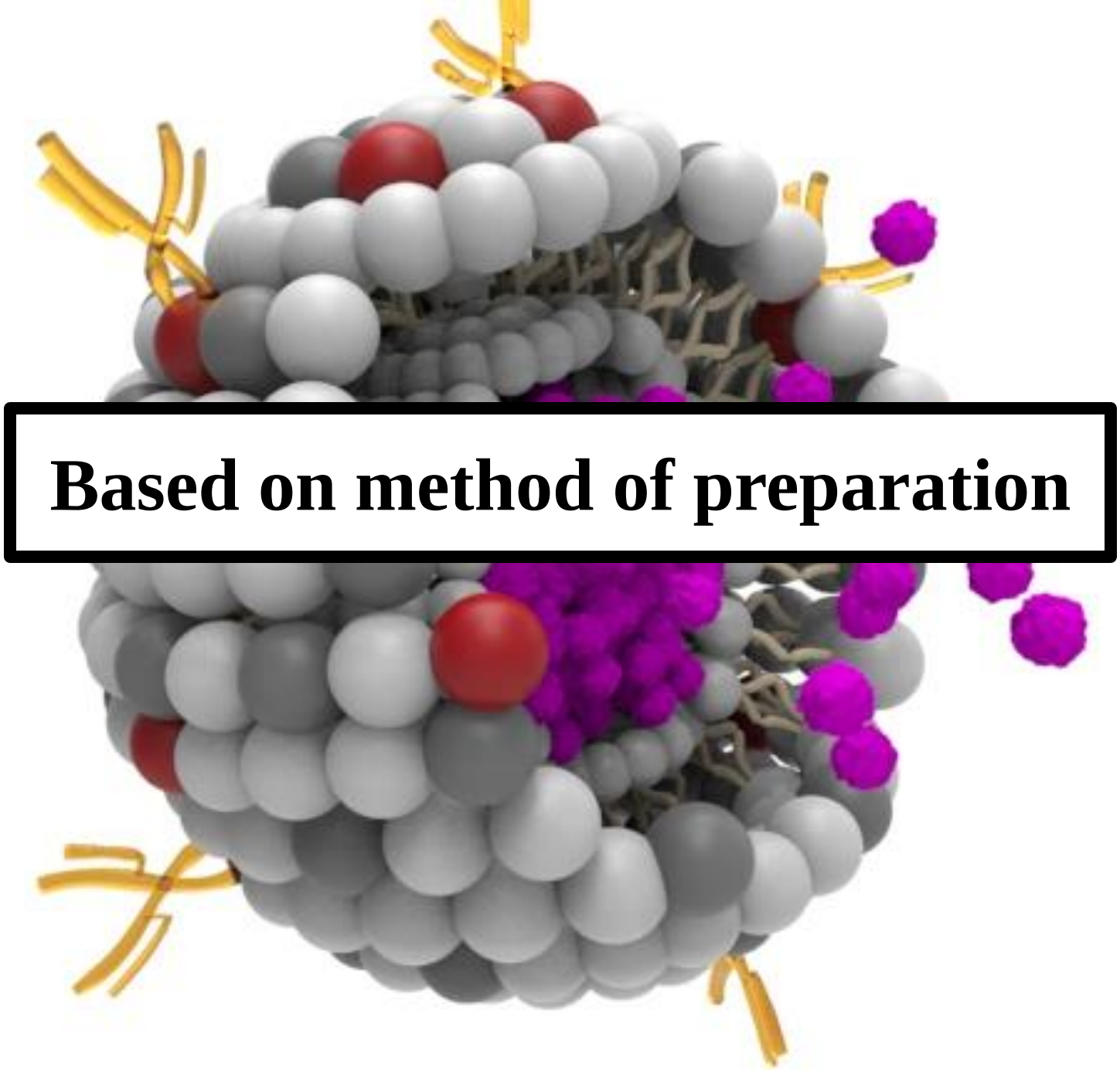
SUV
(Small)

MUL
(Medium)

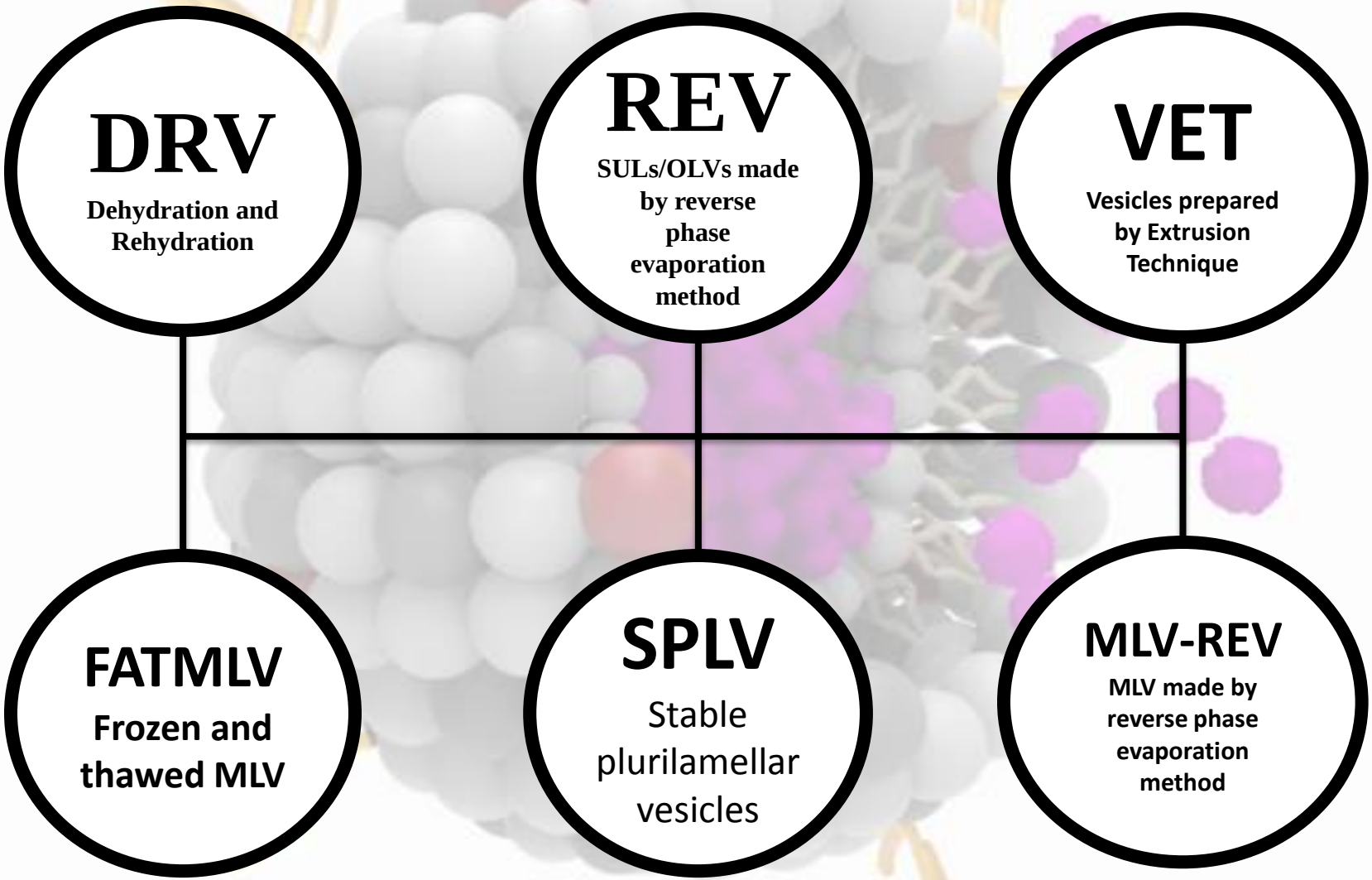
LUV
(Large)

GUV
(Gaint)
1μm

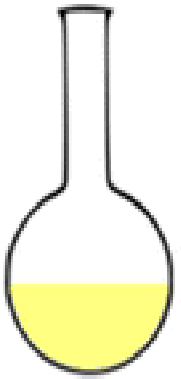

lipid bilayer
MLV
MVV
LUV
SUV
ULV



Based on method of preparation

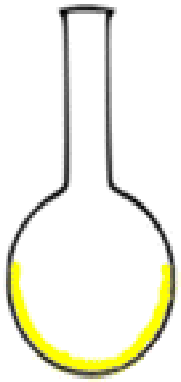

DRV
Dehydration and Rehydration
REV
SULs/OLVs made by reverse phase evaporation method
VET
Vesicles prepared by Extrusion Technique
FATMLV
Frozen and thawed MLV
SPLV
Stable plurilamellar vesicles
MLV-REV
MLV made by reverse phase evaporation method

•**A Cheap and Convenient Method of Liposome Preparation Using Glass Beads as a Source of Shear Force ,** Aoke Wang ,Aftab Ahmad, Sadeeq Ullah, Li Cheng,Lin Ke , Qipeng Yuan (2017)

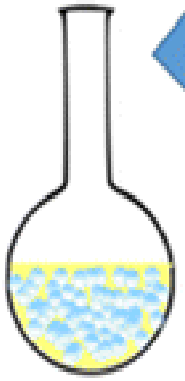


Use the chloroform to dissolve the phospholipids and the cholesterin.

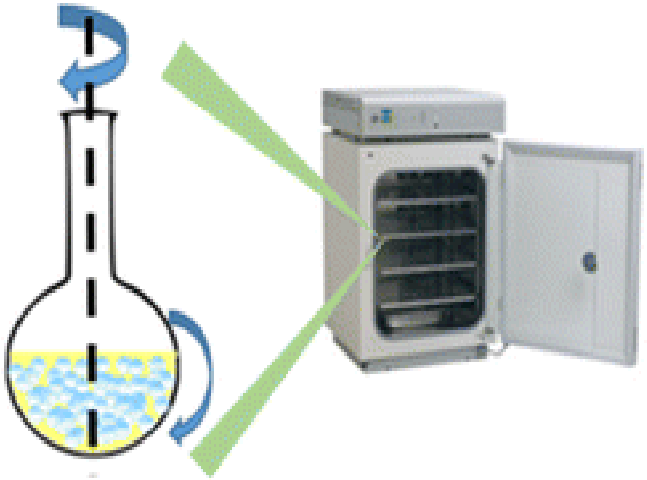
Remove the organic solvent by rotary evaporator.



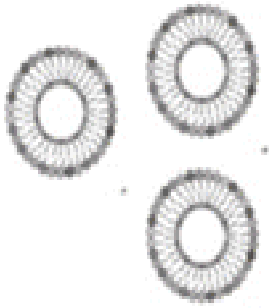
Form an uniform thin film on the wall of the flask.



Add the drug solution with the glass beads into the flask.



Control the size of the liposomes by constant temperature shaker .



Get the nano scale liposomes.

Methode Of liposom Prepration

Passive loading Technique
(during)

Mechanical Dispersion Methodes

- Lipid film hydration by hand shaking non-hand shaking or freeze drying(*t*-butanol)
- Micro emulsification
- Sonocation
- French pressure cell
- Membrane extrusion
- Dried reconstituted vesicles
- Freeze thawed liposomes

Solvent Dispersion Methodes

- Ethanol injection
- Ether injection
- Double emulsion vesicles
- Reverse phase evaporation vesicles
- Stable plurilamellar vesicles

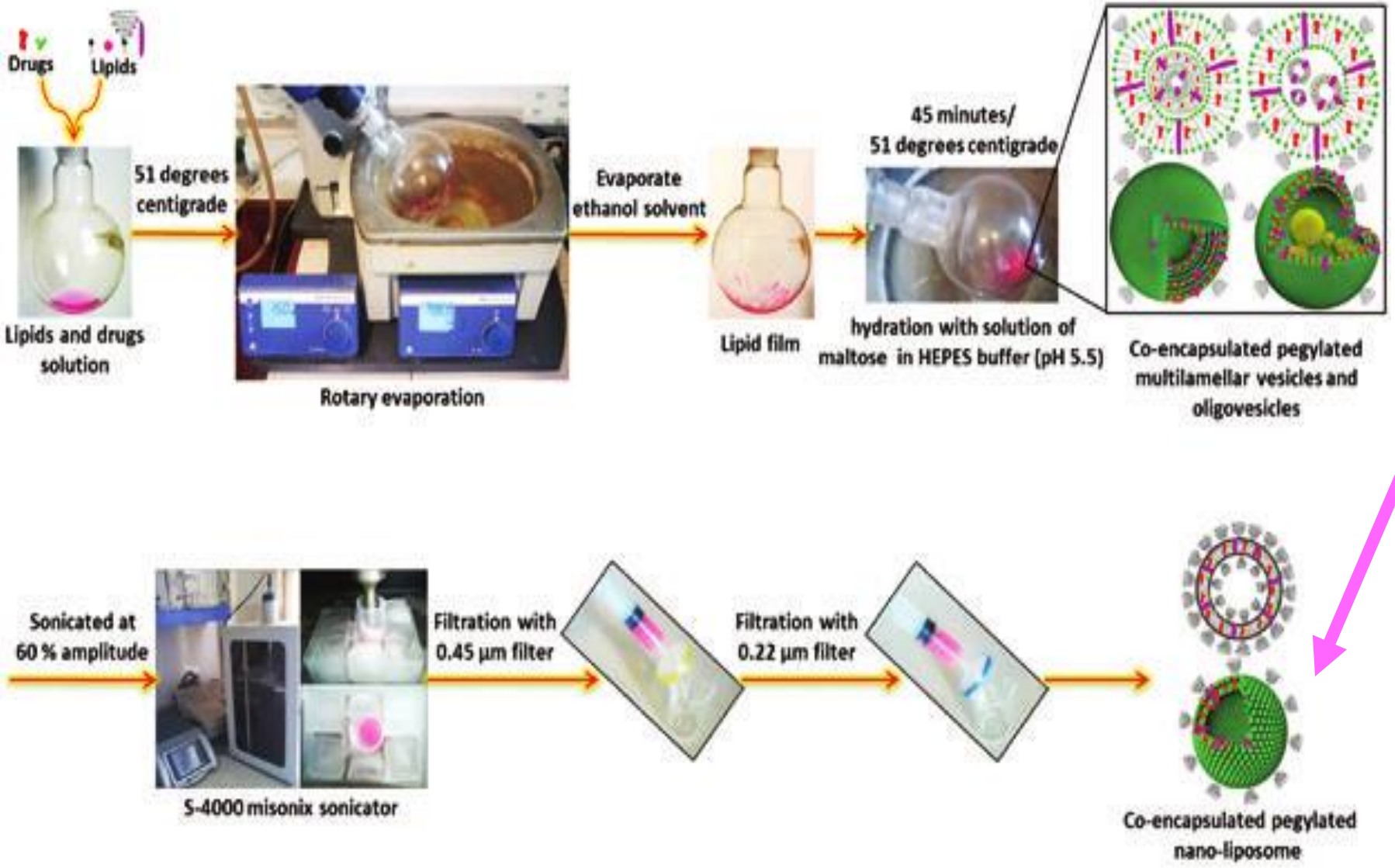
Active Loading Technique
(after)

Detergent Removal Methodes

- **Detergent (cholate ,alkylglycoside,Triton x-100) removal from mixed micellesby:**

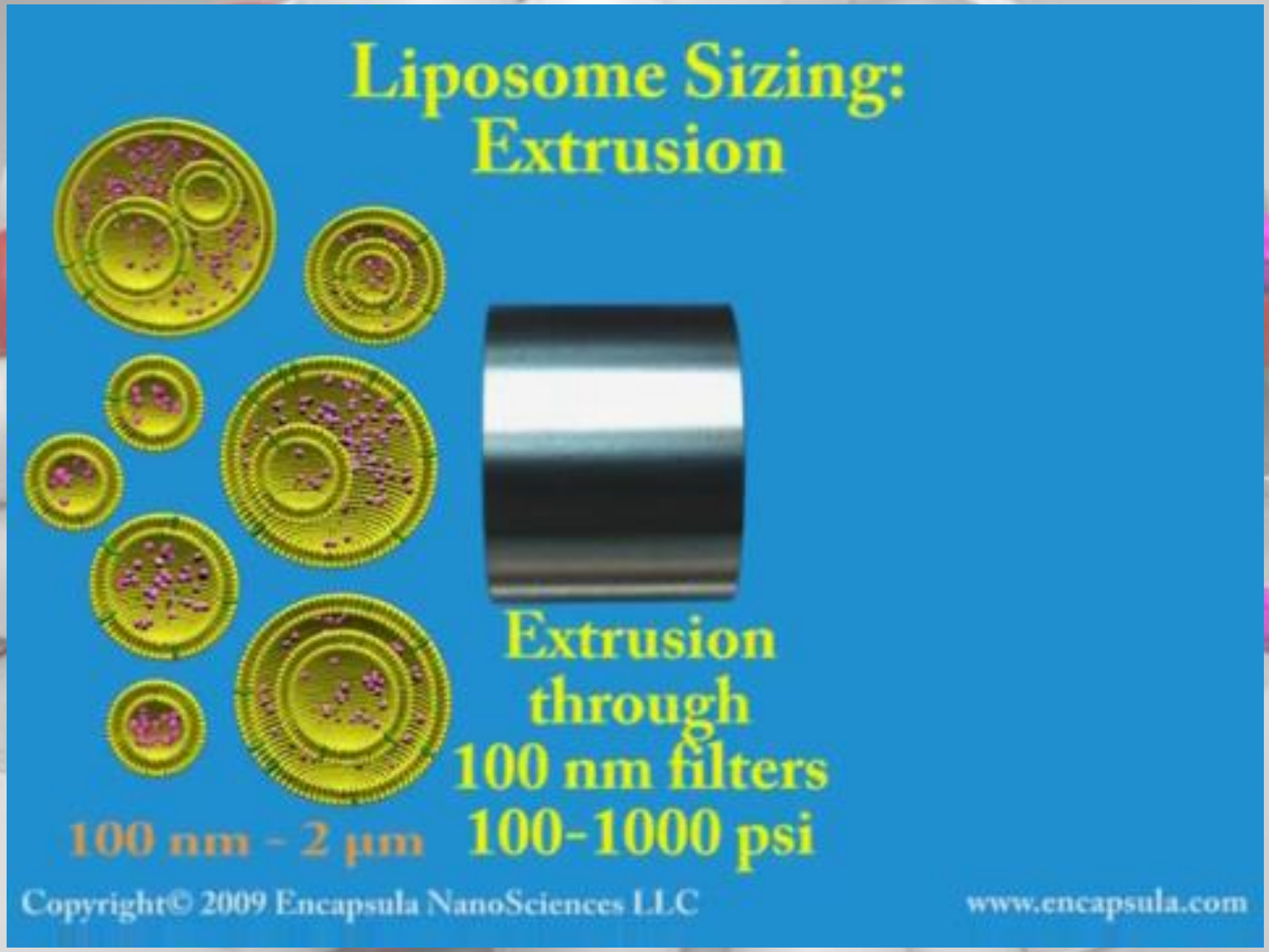
✓ Dialysis
✓ Column chromatogeraphy
✓ Dilution
✓ Reconstituted sandal virus enveloped vesicles

the preparation process of co-encapsulated Nano-liposomes



https://www.researchgate.net/Schematic-model-for-the-preparation-process-of-co-encapsulated-nano-liposomes_fig1_305375457 [accessed 5 Jul, 2018]

https://www.youtube.com/results?search_query=Liposome+Basics-Part+two



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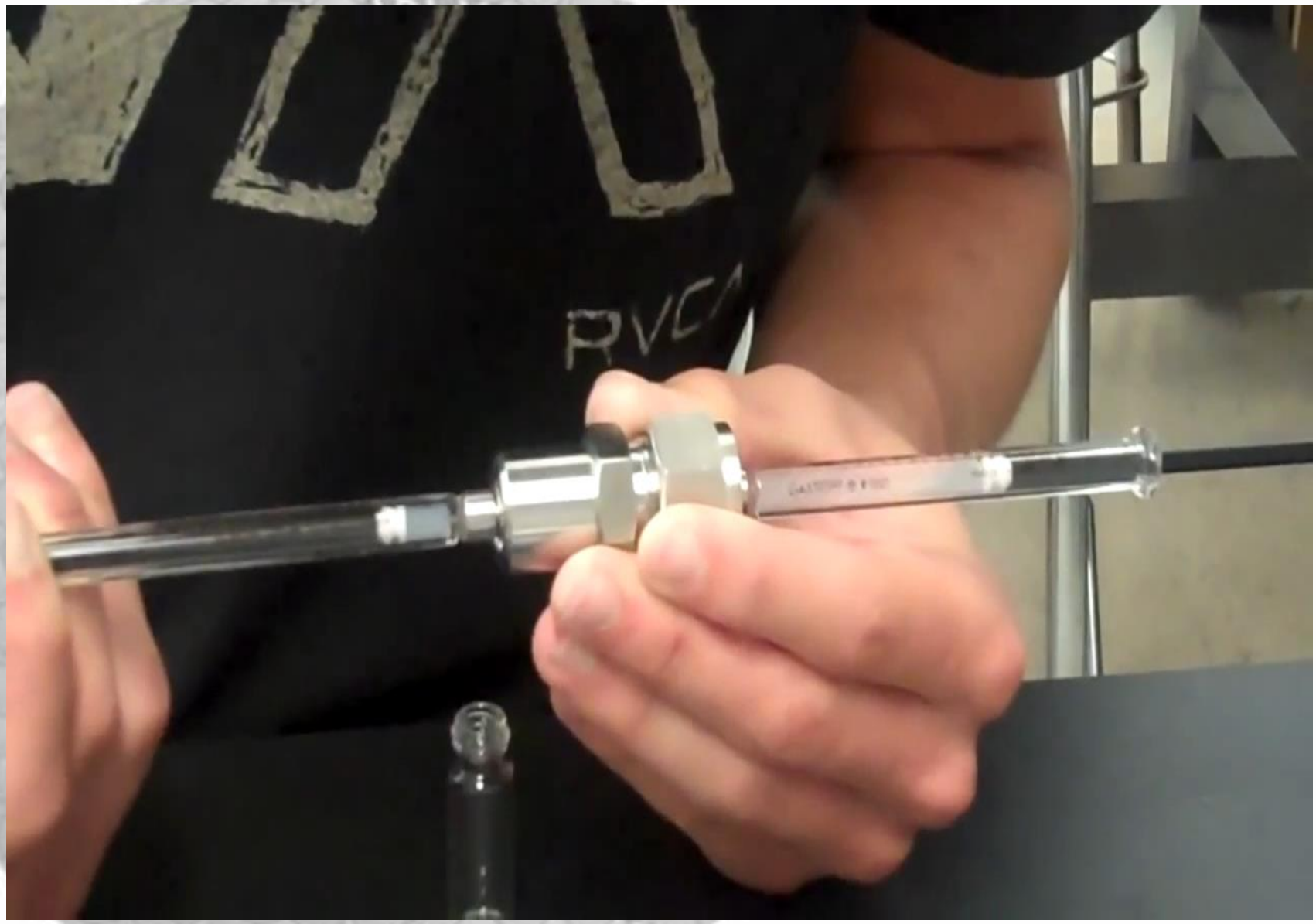

RVCA

Physical Characterization

Parameter	Characterization method
Vesicle shape and surface morphology	Transmission Electron Microscopy, Freeze-fracture electron microscopy
Mean vesicle size and size Distribution	Dynamic light scattering, zetasizer, Photon correlation spectroscopy, laser light scattering, gel permeation and gel exclusion
Surface charge	Free-flow electrophoresis
Electrical surface potential and surface pH	Zeta potential measurements & pH sensitive probes
Percent of free drug/ percent capture	Mini column centrifugation, ion-exchange Chromatography , radiolabelling
Drug release	Diffusion cell/ dialysis

Chemical Characterization

Parameter	Characterization method
Phospholipid concentration	Barlett assay, stewart assay, **HPLC**
Cholesterol concentration	Cholesterol oxidase assay and HPLC
Phopholipid peroxidation	UV absorbance, Iodometric and GLC
Phospholipid hydrolysis, Cholesterol auto-oxidation	HPLC and TLC
Osmolarity	**Osmometer**

Biological Characterization

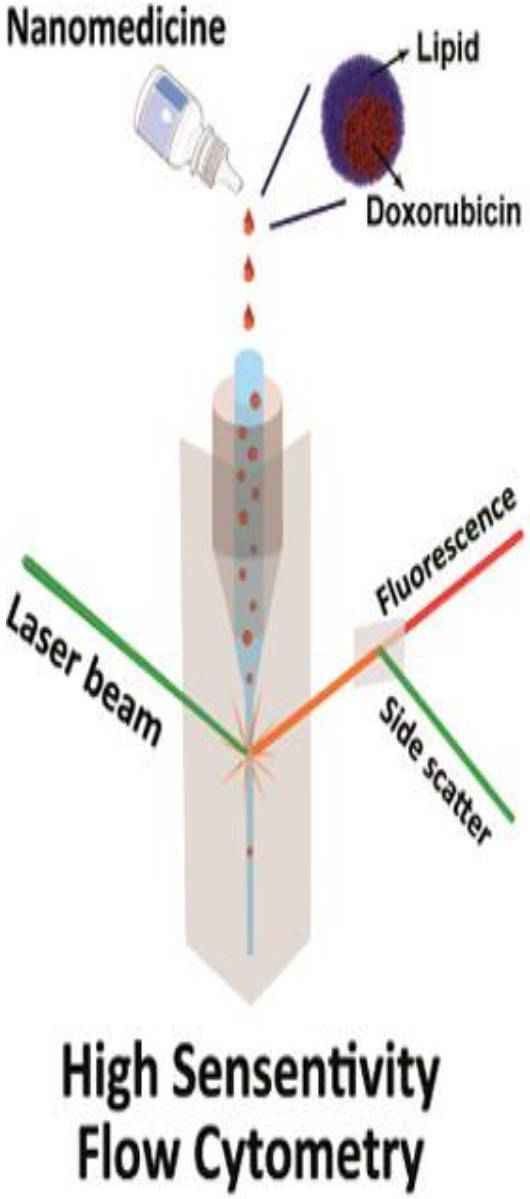
Parameter	Characterization method
Sterility	Aerobic or anaerobic cultures
Pyrogenicity	Limulus Amebocyte Lysate (LAL) test
Animal toxicity	Monitoring survival rates, **histology and pathology**

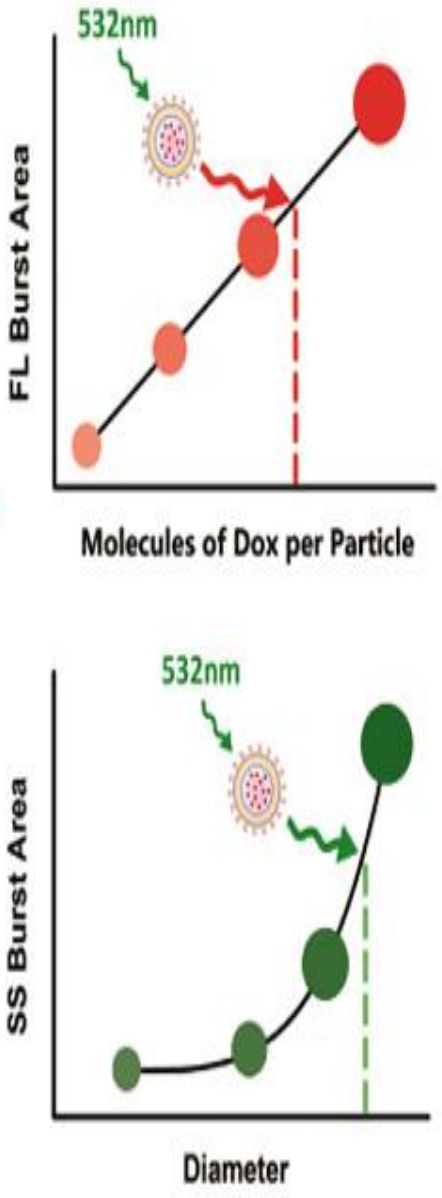
Flow Cytometry with Fluorescent Dyes

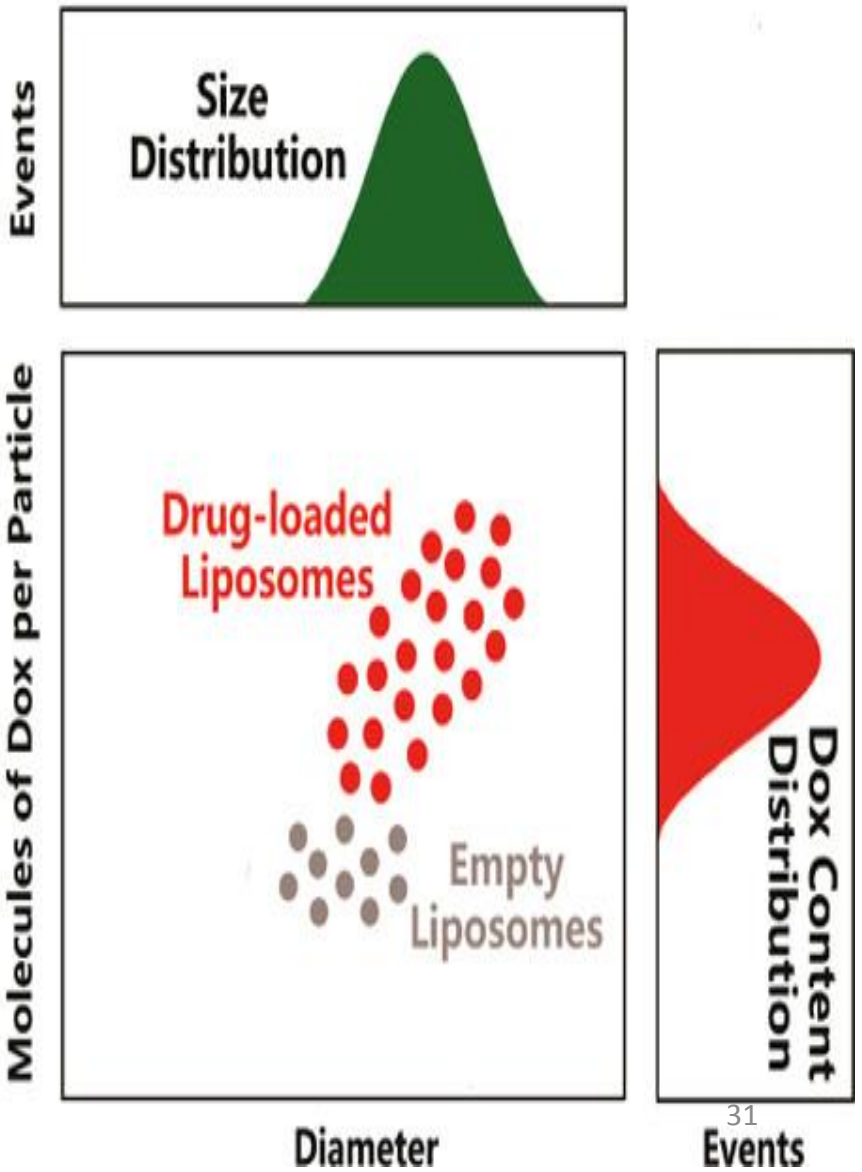
fast and reliable method

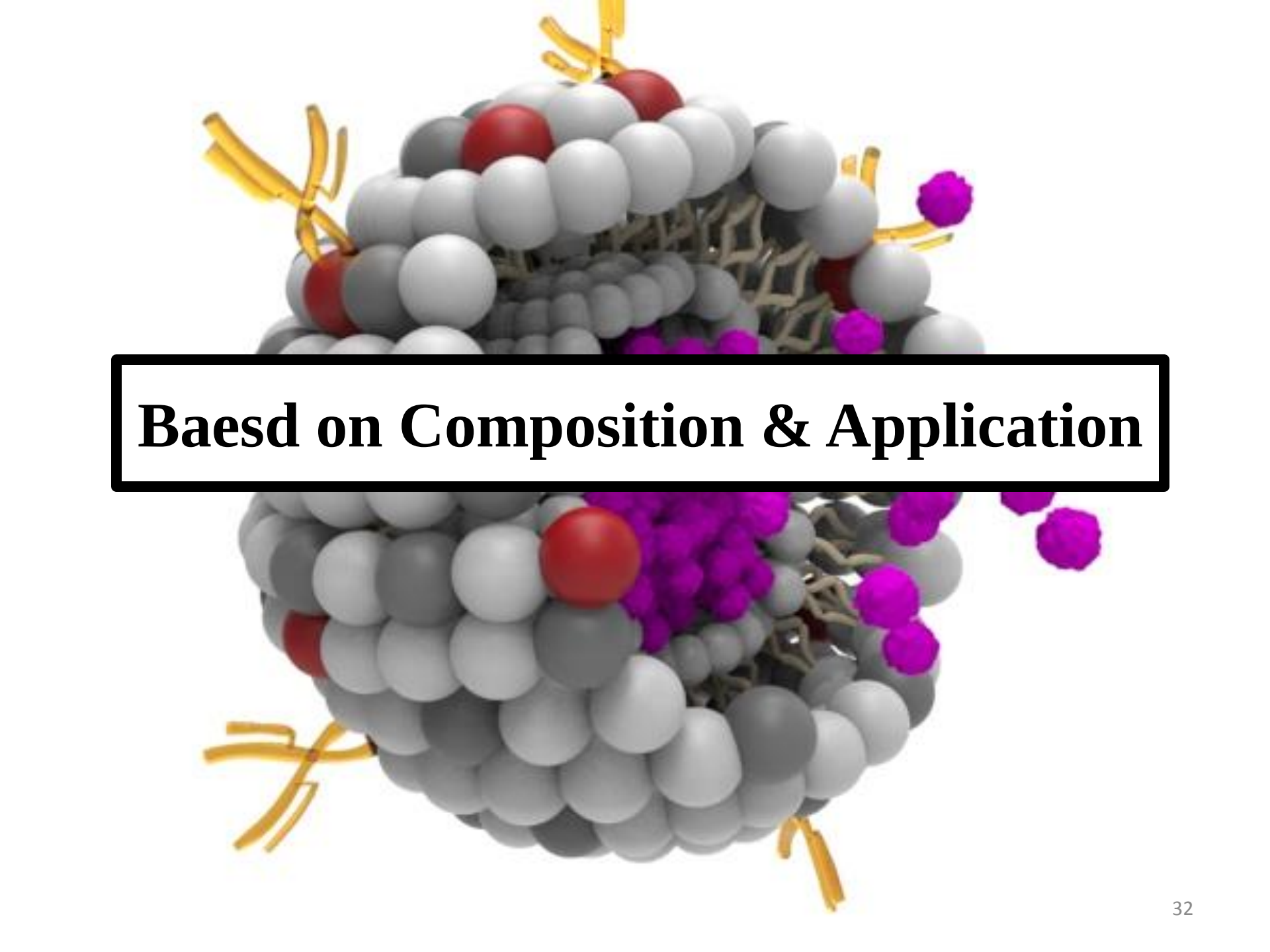
for liposomes assessment [5]

Measurement particle size and drug content (36)

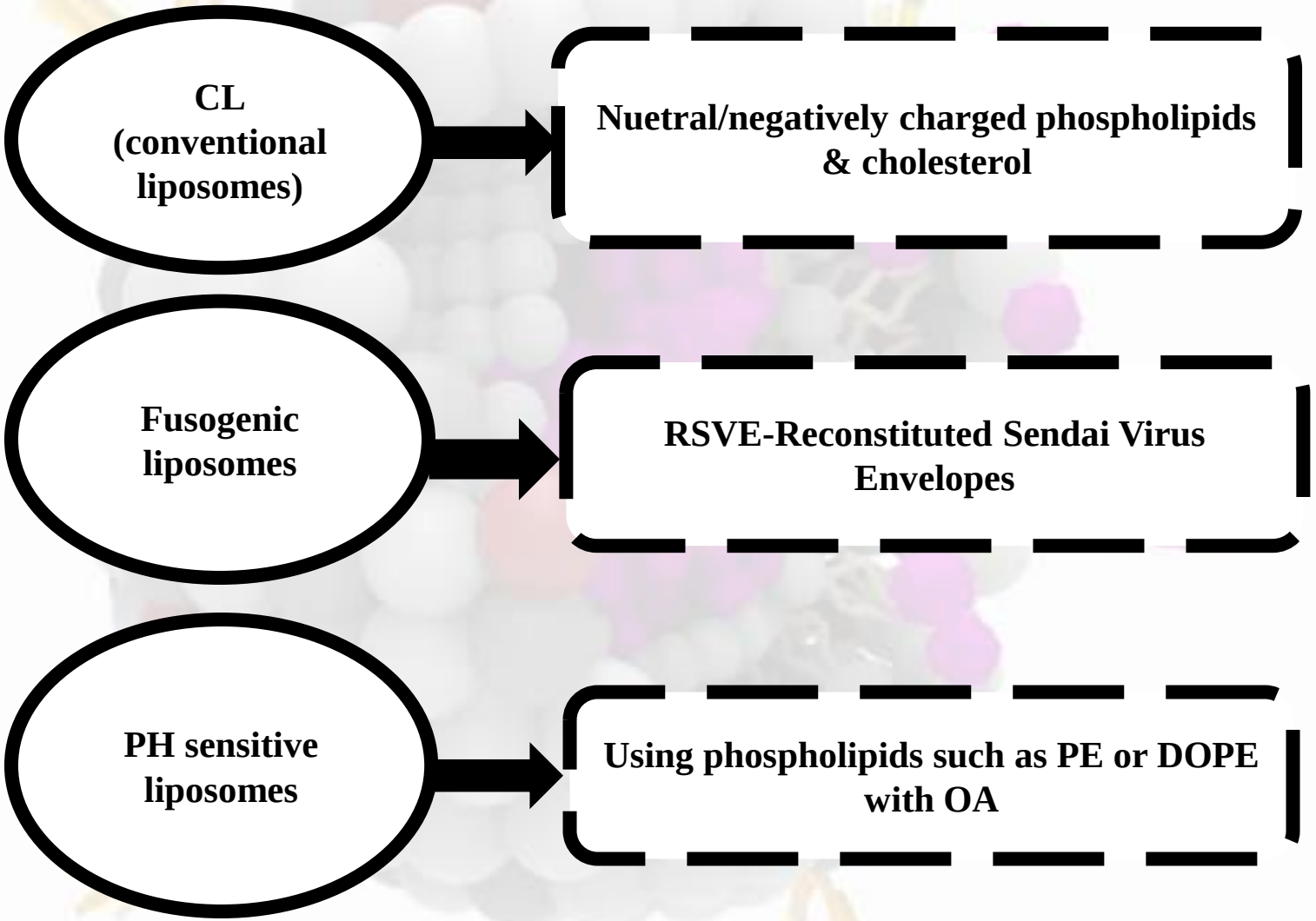


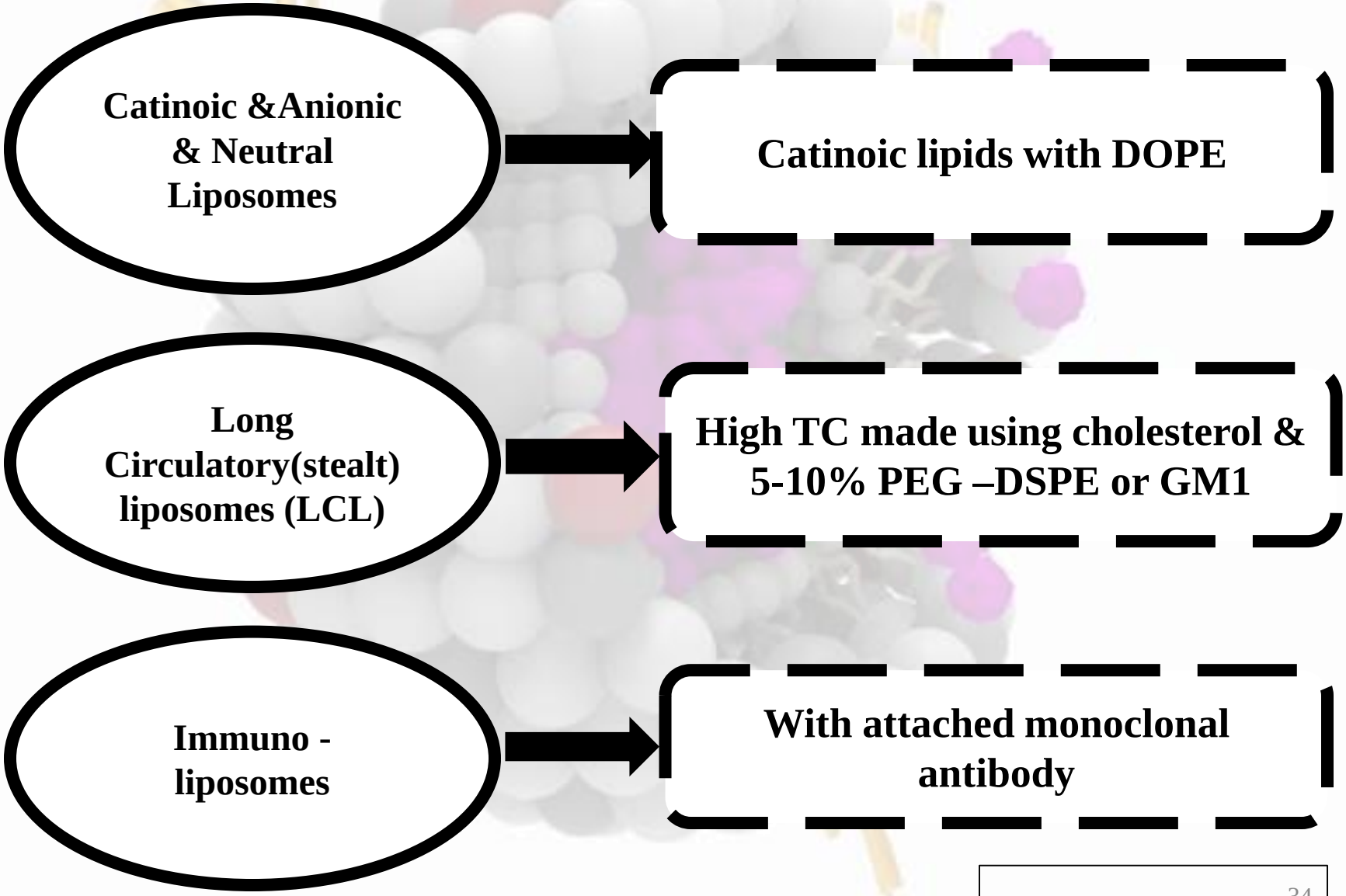




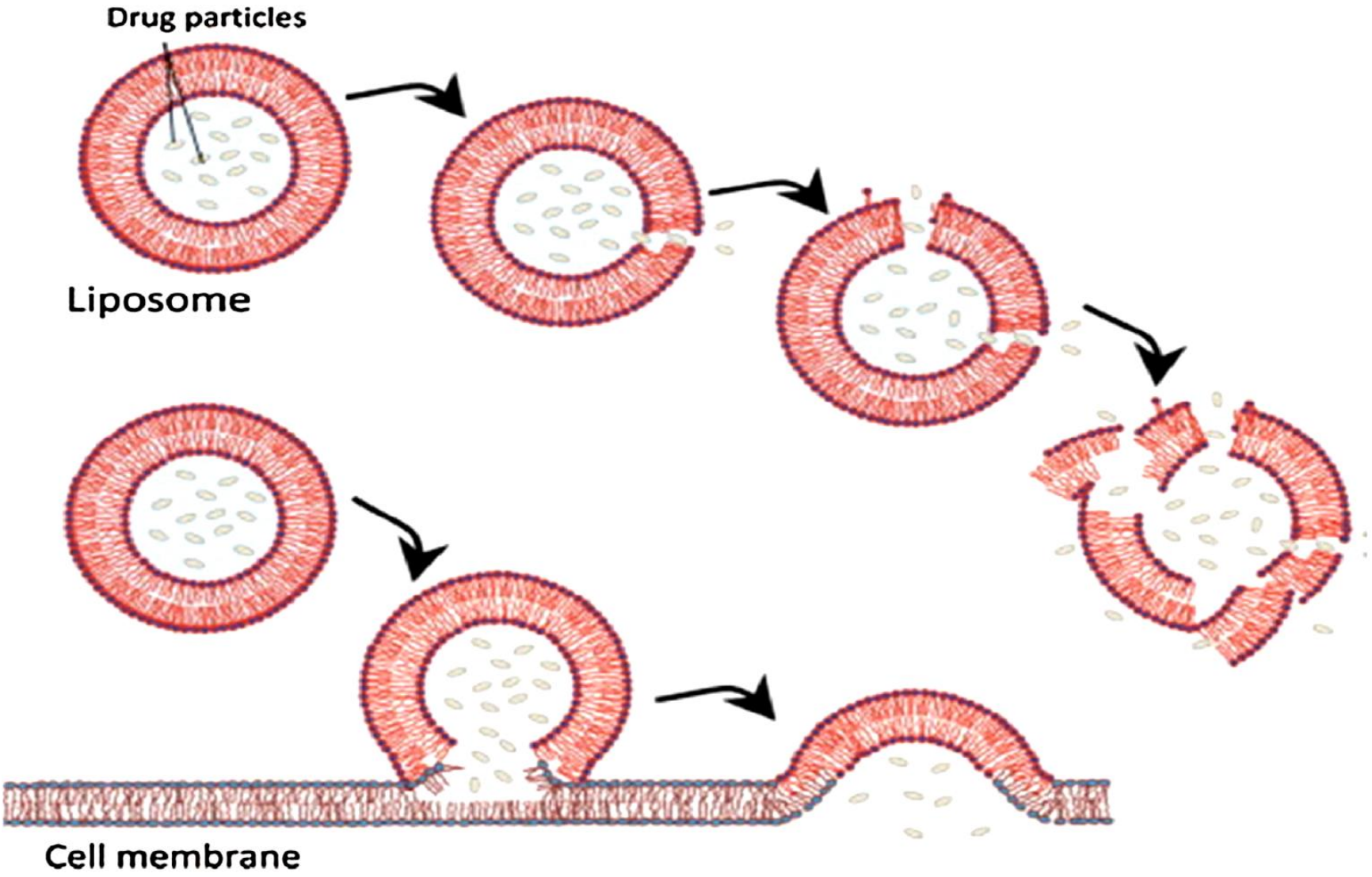


Baesd on Composition & Application

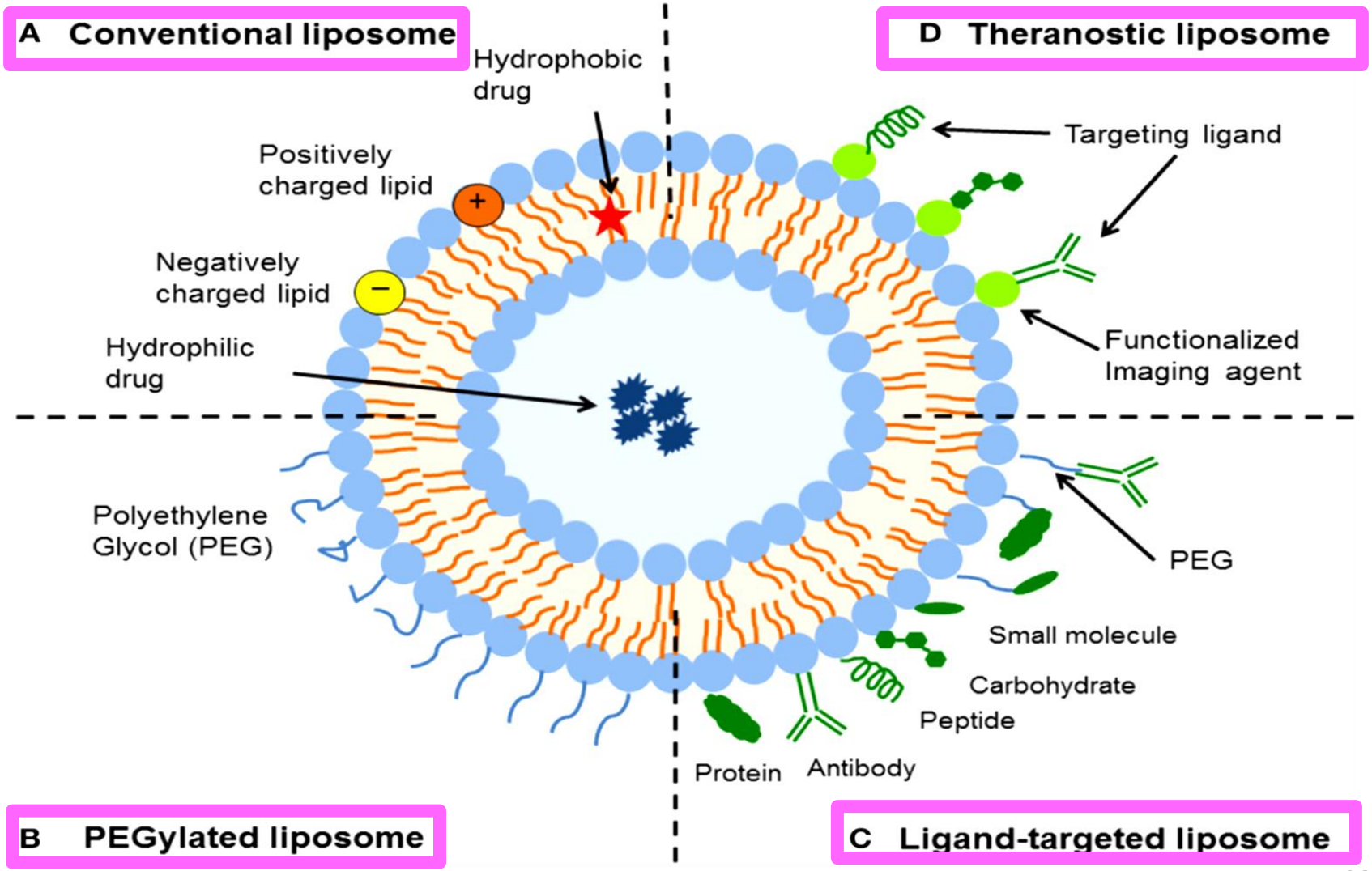

CL
(conventional
liposomes)
Nuetral/negatively charged phospholipids
& cholesterol
Fusogenic
liposomes
RSVE-Reconstituted Sendai Virus
Envelopes
PH sensitive
liposomes
Using phospholipids such as PE or DOPE
with OA


Catinoic &Anionic & Neutral Liposomes
Catinoic lipids with DOPE
Long Circulatory(stealt) liposomes (LCL)
High TC made using cholesterol & 5-10% PEG –DSPE or GM1
Immuno - liposomes
With attached monoclonal antibody

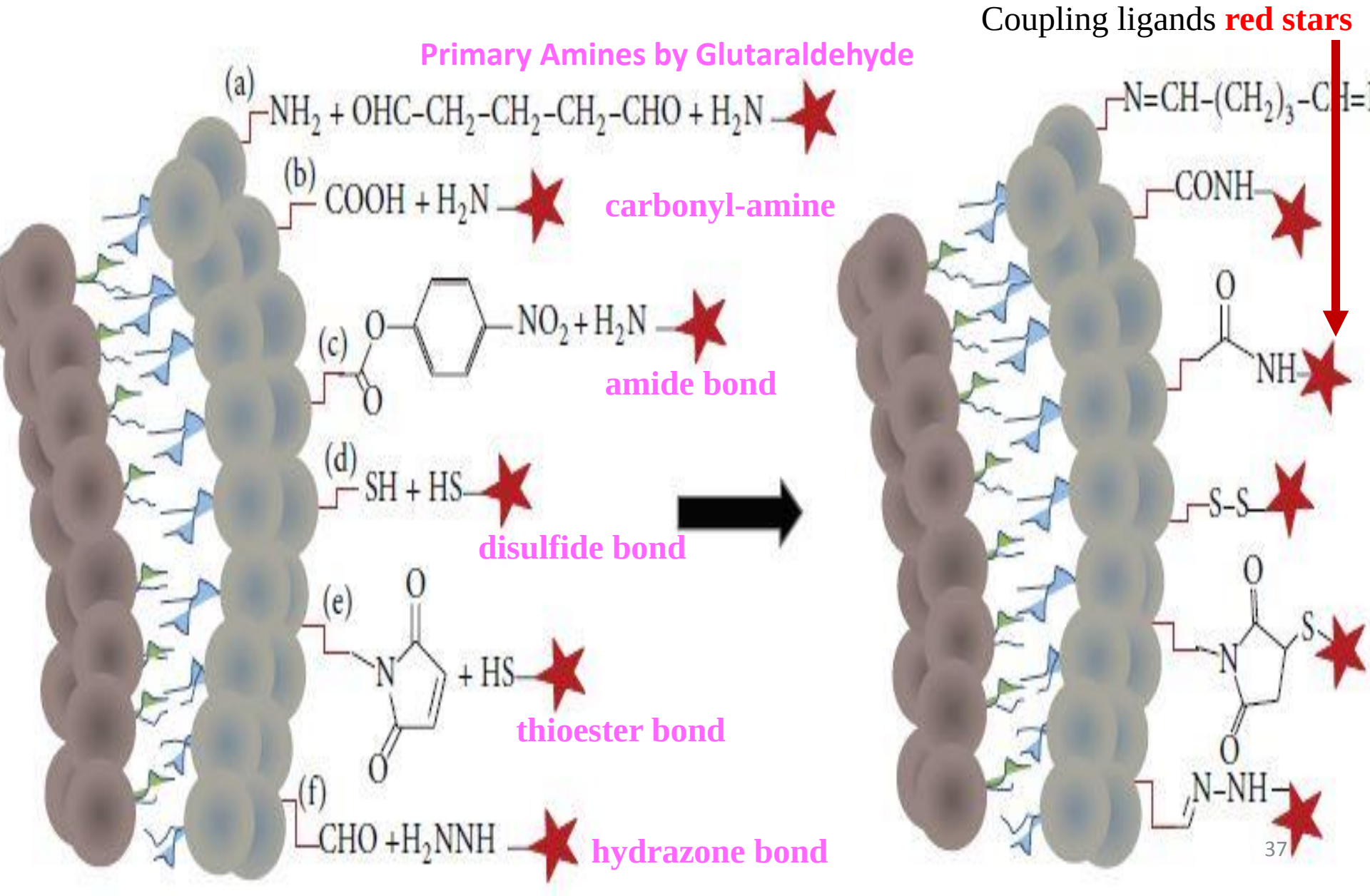
Drug delivery by liposomes (14)



Types Of Liposomal Drug Delivery Systems[4]



Classical methods for coupling ligands(17)



PEG (polyethylene glycol)(4)

- The Hydrophilic Polymer ,Obtaining Sterically-stabilized Liposomes
- Reduce *Invivo* **Opsonization**
- Reduce Rapid Recognition **RES** .
- Half-lives (**2 - 24 h**) In Rodents , (**45 h**) In Humans
- Reduced **EPR** Effects

(ABC) Phenomenon[4]

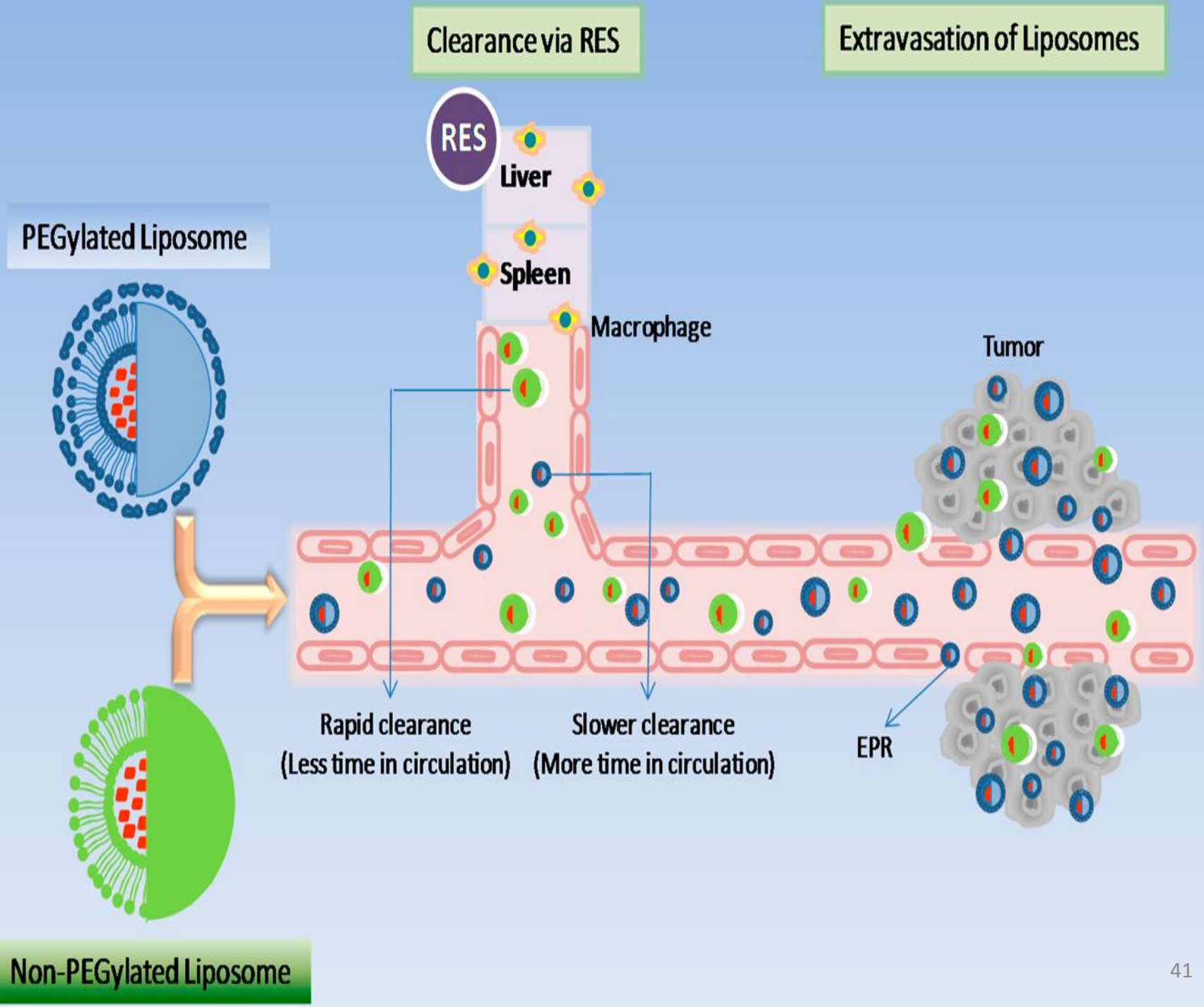
- Accelerated Blood Clearance
- Repeated injection of PEGylated liposomes (long circulating properties)
- **Affected by :**

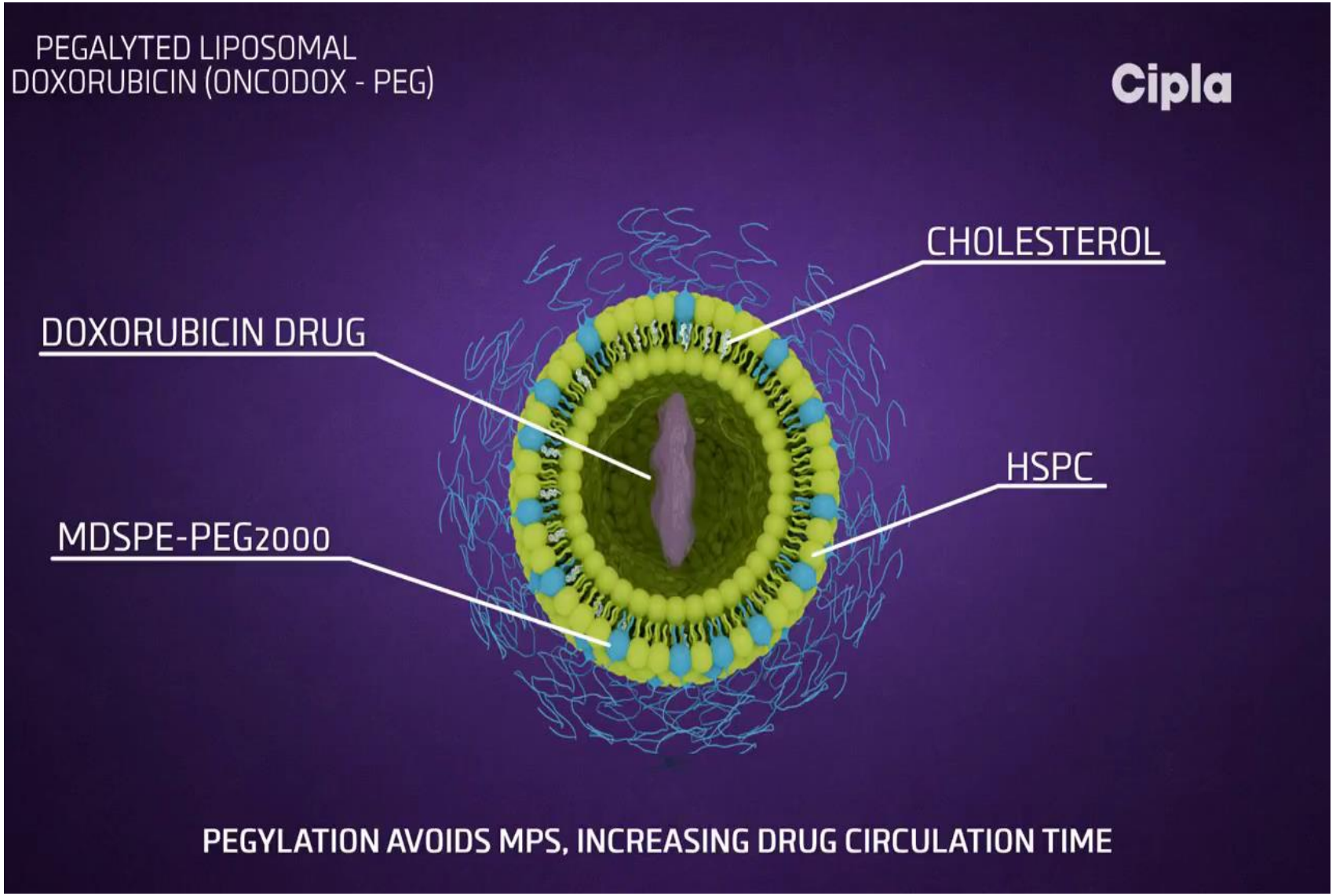
a. Lipid dose
b. PEG surface density
c. The interval between the first and consecutive injections

Table 2

Clearance times.

Nano carrier systems	CircT½
PEGylated liposomes	~ 5 – 15 h
Non-PEGylated liposomes	< 1 h
Polymersomes (ps)	≤ 30 h
Polystyrene flattened disks (0.1 × 1 ×3 μm)*	< 1 h
Polystyrene 100 ran spheres*	< 1 h
Micro/nan ofabricated (PRINT)	< 1 h
Filomicelle	≤ 1 wk
Carbon nanotube (CNT)	≤ 3 h


Clearance via RES
Extravasation of Liposomes
RES
Liver
Spleen
Macrophage
PEGylated Liposome
Tumor
Rapid clearance
(Less time in circulation)
Slower clearance
(More time in circulation)
EPR
Non-PEGylated Liposome



https://www.youtube.com/watch?v=vUqwIL5lgS8

Cationic liposomes

- **In Gene Delivery :**

✓ **cancer Treatment (RGD -cationic for angiogenes inhibition)(9)**

✓ **Designed Anti oxidant Lipid (Treating ROS Related Diseases)(10)**

✓ **With Poly hydroxyl (combine with DNA and lipoplexes(**A complex of DNA and liposome **)) (11)**

- **In Gene Therapy :**

✓ **AS Non Viral Vector : (CRISPR/Cas9 gene-editing systems)[12]**

✓ **Induced cell Necrosis[18]**

✓ **As Carrier For plasmid DNA , siRNA and miRNA [12]**

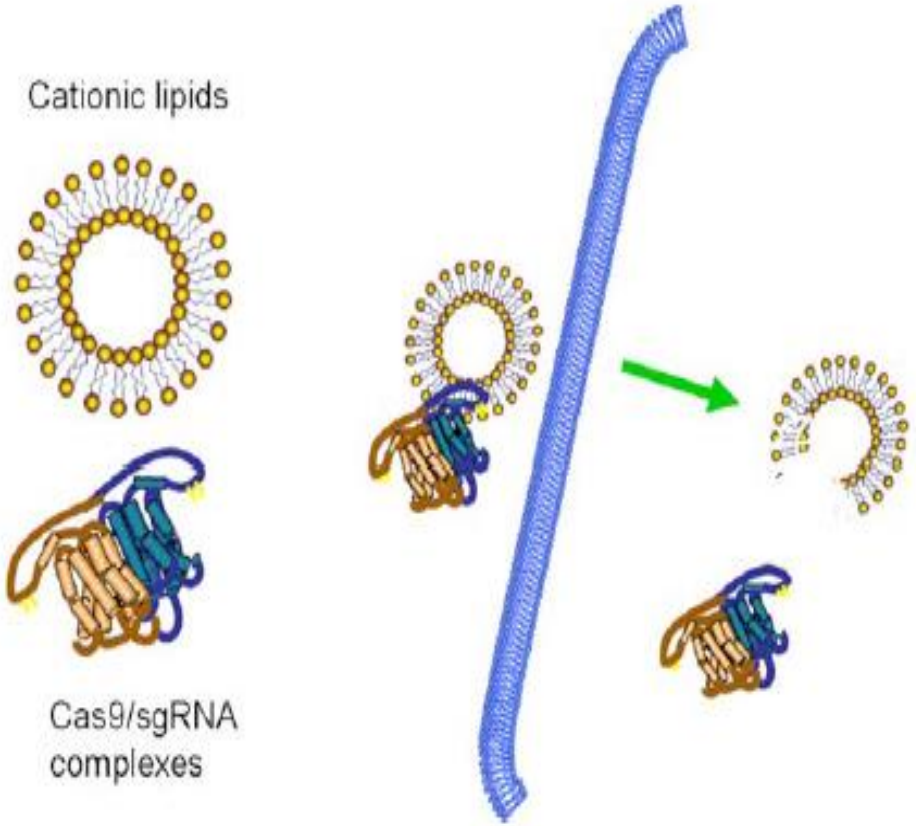


Figure 2 Non-viral gene delivery systems of CRISPR/Cas9 gene-editing systems. The example shown depicts a pre-loaded ribonucleoprotein, consisting of the Cas9 enzyme with sgRNA already bound. This Cas9-sgRNA complex then interacts with cationic lipids, which facilitate cell entry.

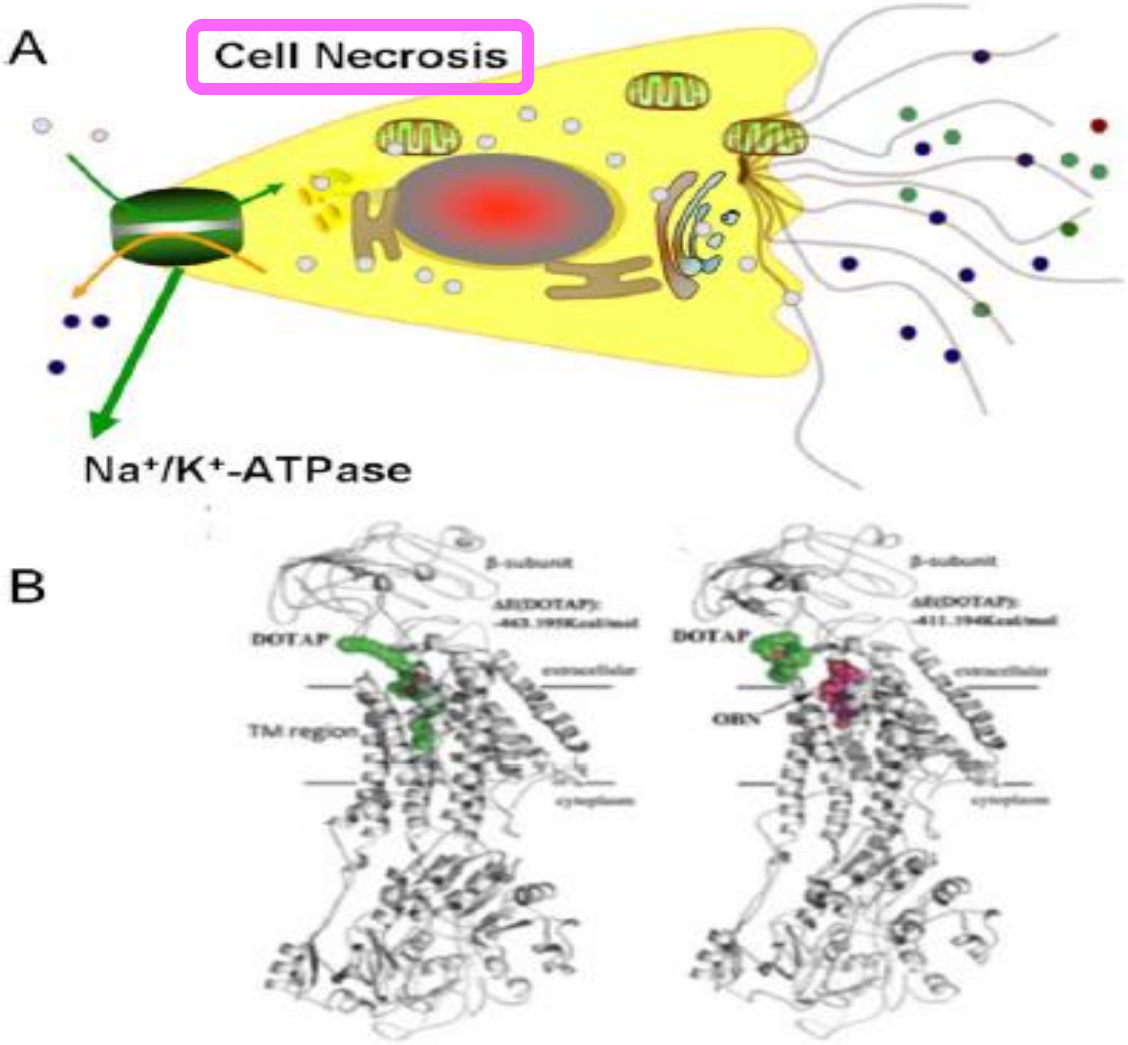


Figure3 (A Cationic nanocarrier-induced cell necrosis. Cationic nanocarriers could interact with the cation-binding site of Na^+/K^+-ATPase. (B) The complex structures of Na^+/K^+-ATPase-DOTAP and Na^+/K^+-ATPase-ouabain/DOTAP were calculated (Xiawei Wei et al. Cell Res 2015; 25:237-253).

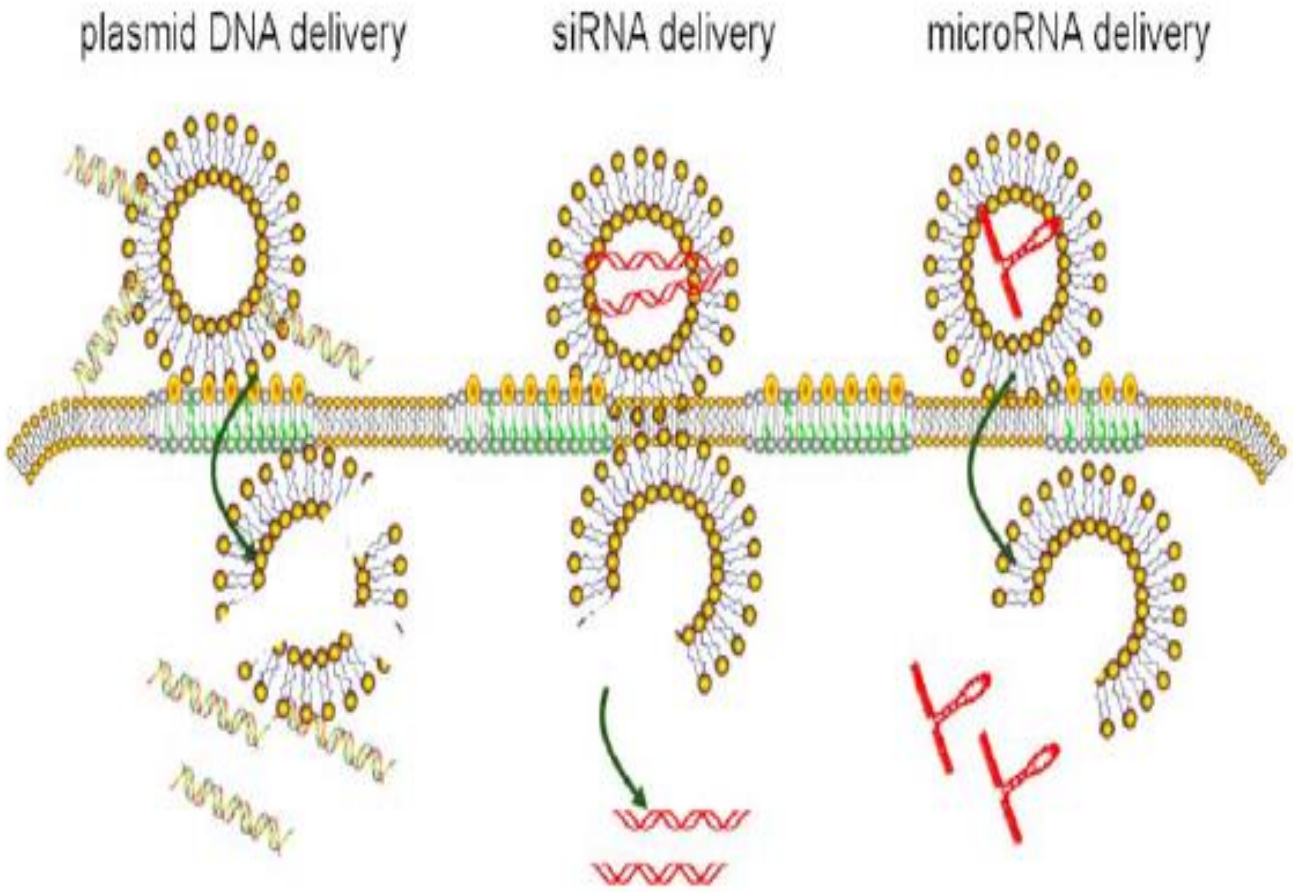
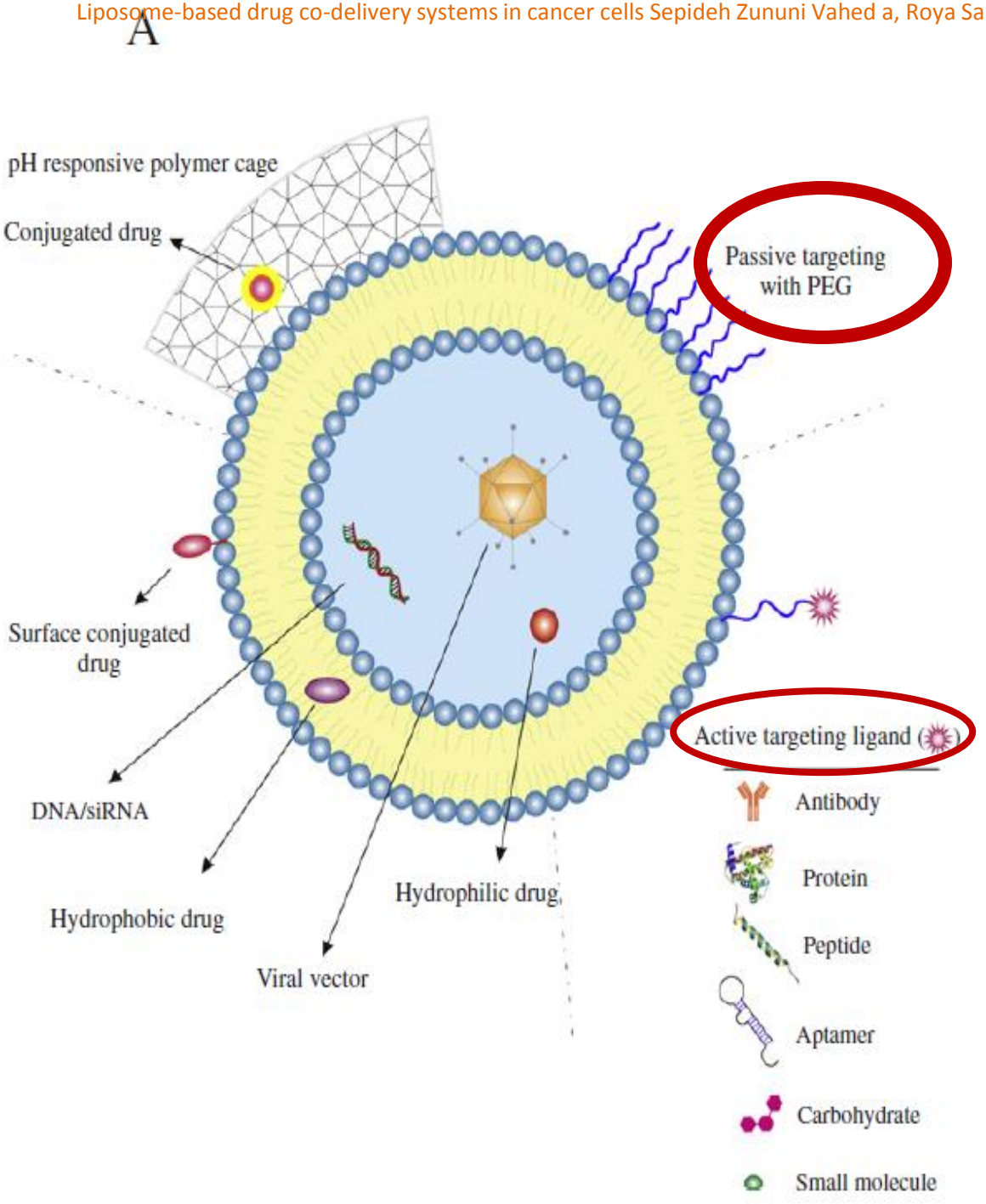


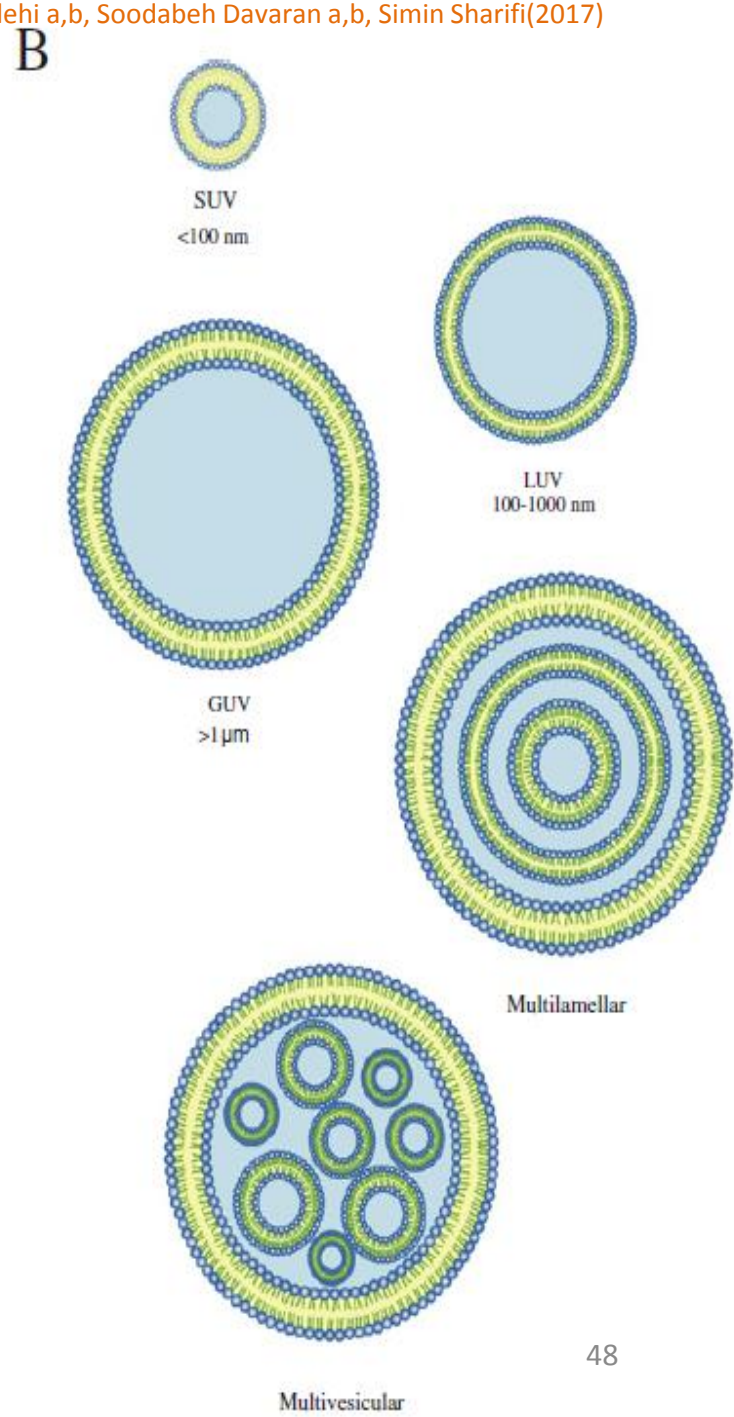
Figure 1 Non-viral delivery systems of gene delivery systems Three examples of non-viral nucleic acid delivery are shown, each complexed to a cationic liposome: plasmid DNA, siRNA and miRNA

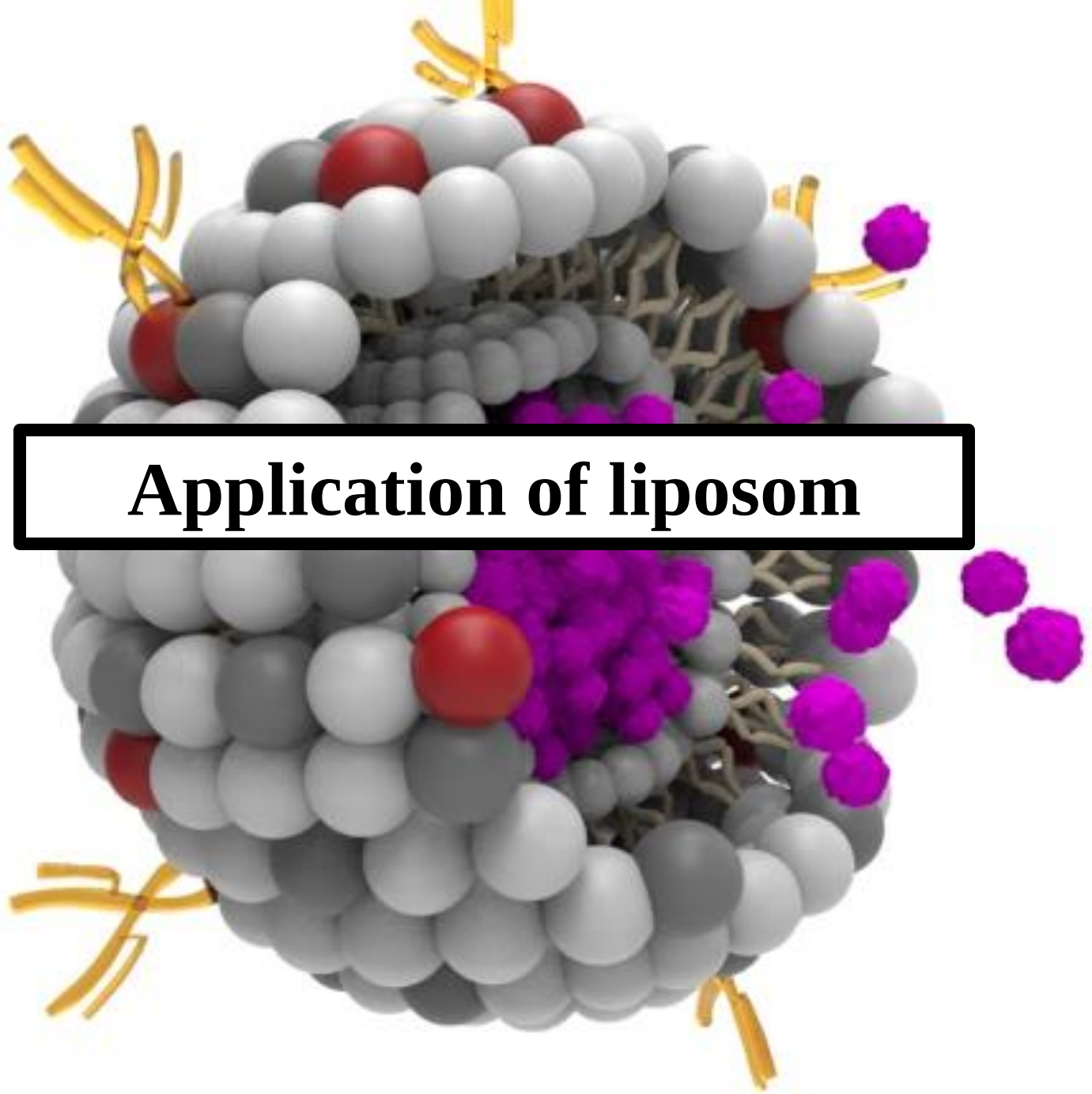
Strategies for overcoming drug resistance using modified liposomes[18]

Strategy	Proposed mechanism
Anionic liposomes Triggered release • Modified liposomes can increase and optimize drug release in target tissue dependent	• Anionic lipids may inhibit PGP • Possible internalization
Other inhibitory lipids	• Certain phospholipids may inhibit PGP
Thermosensitive liposomes	• Modified liposomes can release drug upon hyperthermia treatment
Triggered release	• Modified liposomes can increase and optimize drug release in target tissue dependent on pH or other triggers
Combining liposomes and resistance inhibitors	• Liposomal chemotherapeutic may be better than free drug in combination with resistance inhibitors • Liposome delivery of resistance inhibitors may increase therapeutic index
Delivery of hydrophobic drug analogs	• Liposomes can deliver poorly soluble drugs that are not substrates for PGP
Gene therapy approaches	• Non-viral delivery of nucleic acid-based constructs to tumor cells to reverse, circumvent, or exploit drug resistance • Non-viral delivery of resistance genes to normal tissues to protect them from chemotherapy (“chemoprotection”)

Liposome-based drug co-delivery systems in cancer cells Sepideh Zununi Vahed a, Roya Salehi a,b, Soodabeh Davaran a,b, Simin Sharifi(2017)







Application of liposom

Medical Application of liposom

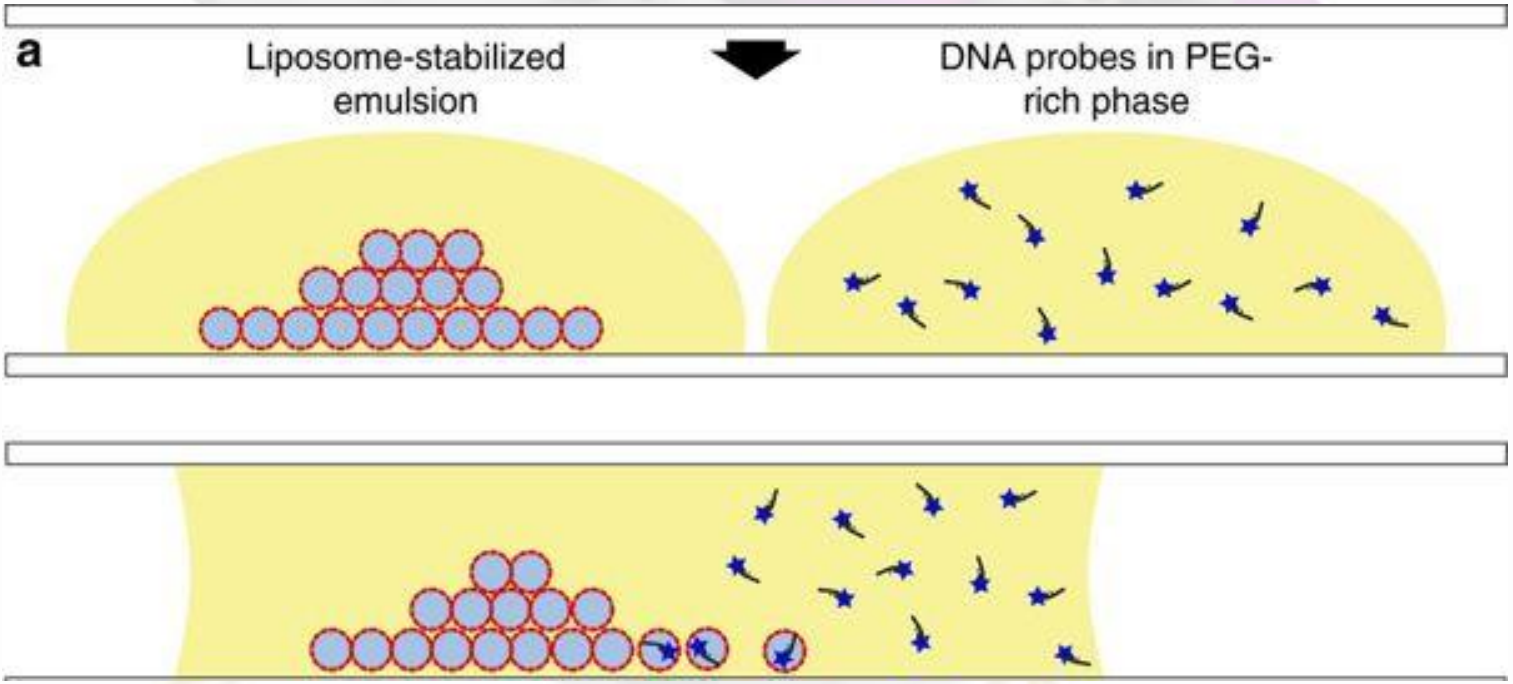
- ✓ treatment of **heavy metal poisoning**
- ✓ Enzyme **Replacement**
- ✓ **Diagnostic** imaging of tumors
- ✓ Cosmetics
- ✓ Study of membranes
- ✓ Drug delivery
- ✓ Bioreactor

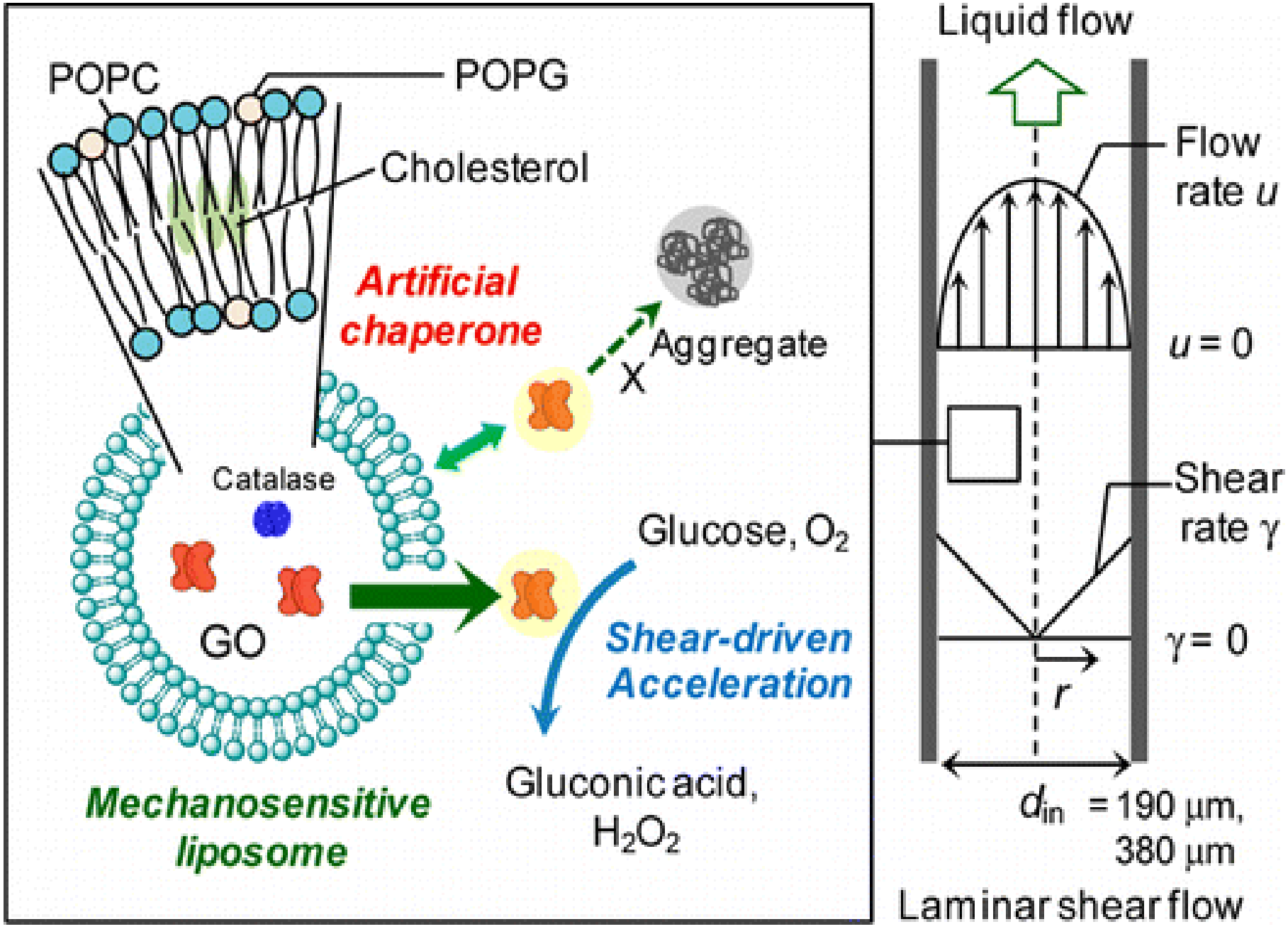
Application of Nanoliposomes in Anesthesia (22)

- ✓ Pain Control
- ✓ **Rapid** Patient **Recovery**
- ✓ Increased Patient Comfort
- ✓ Treatment Costs **Reduction**
- ✓ **Shortens** Length Of **Hospitalization**

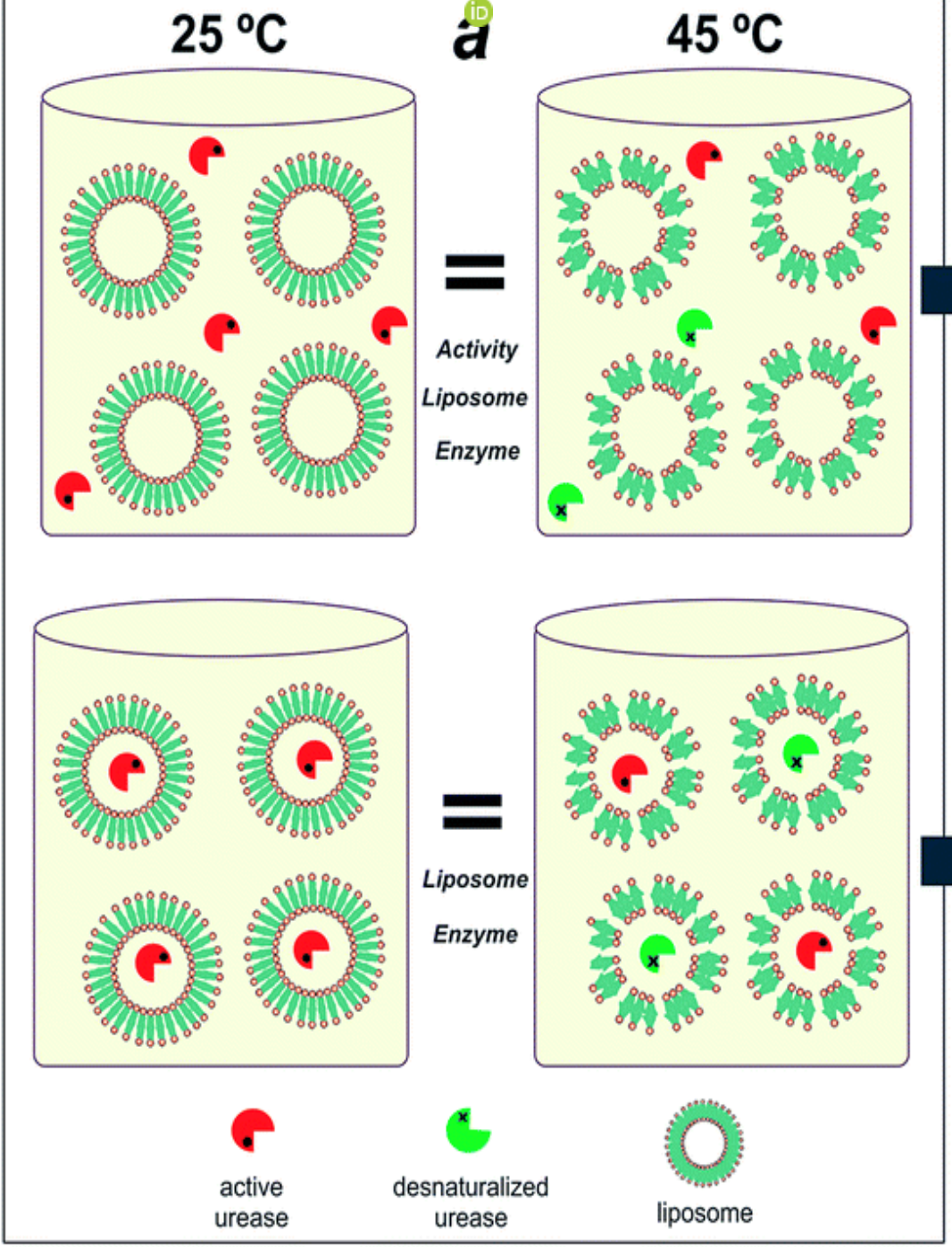
Bioreactors

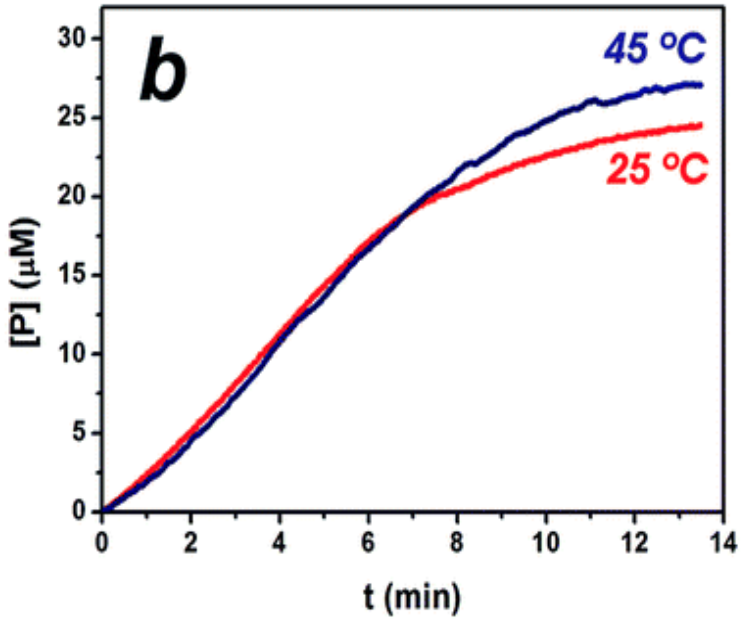
- Liposome used as **Microreactors** (41)
- Application in **biotechnology** & medicine.

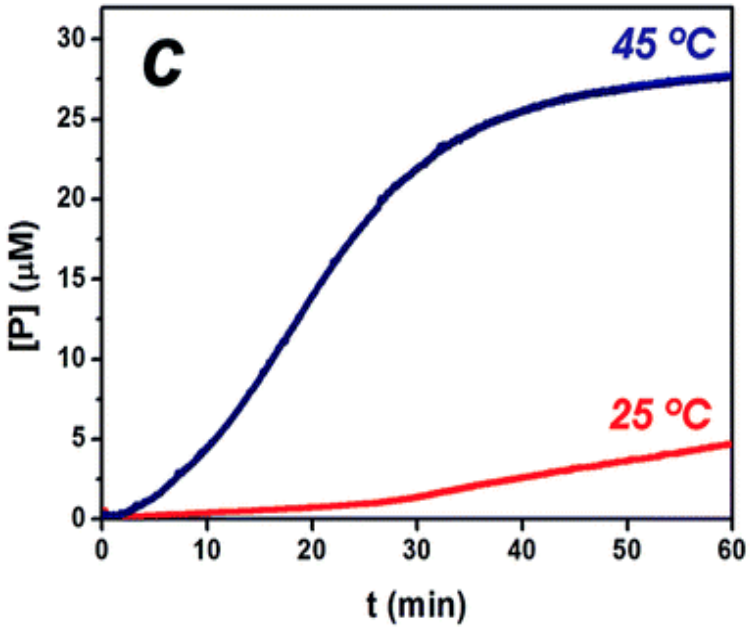




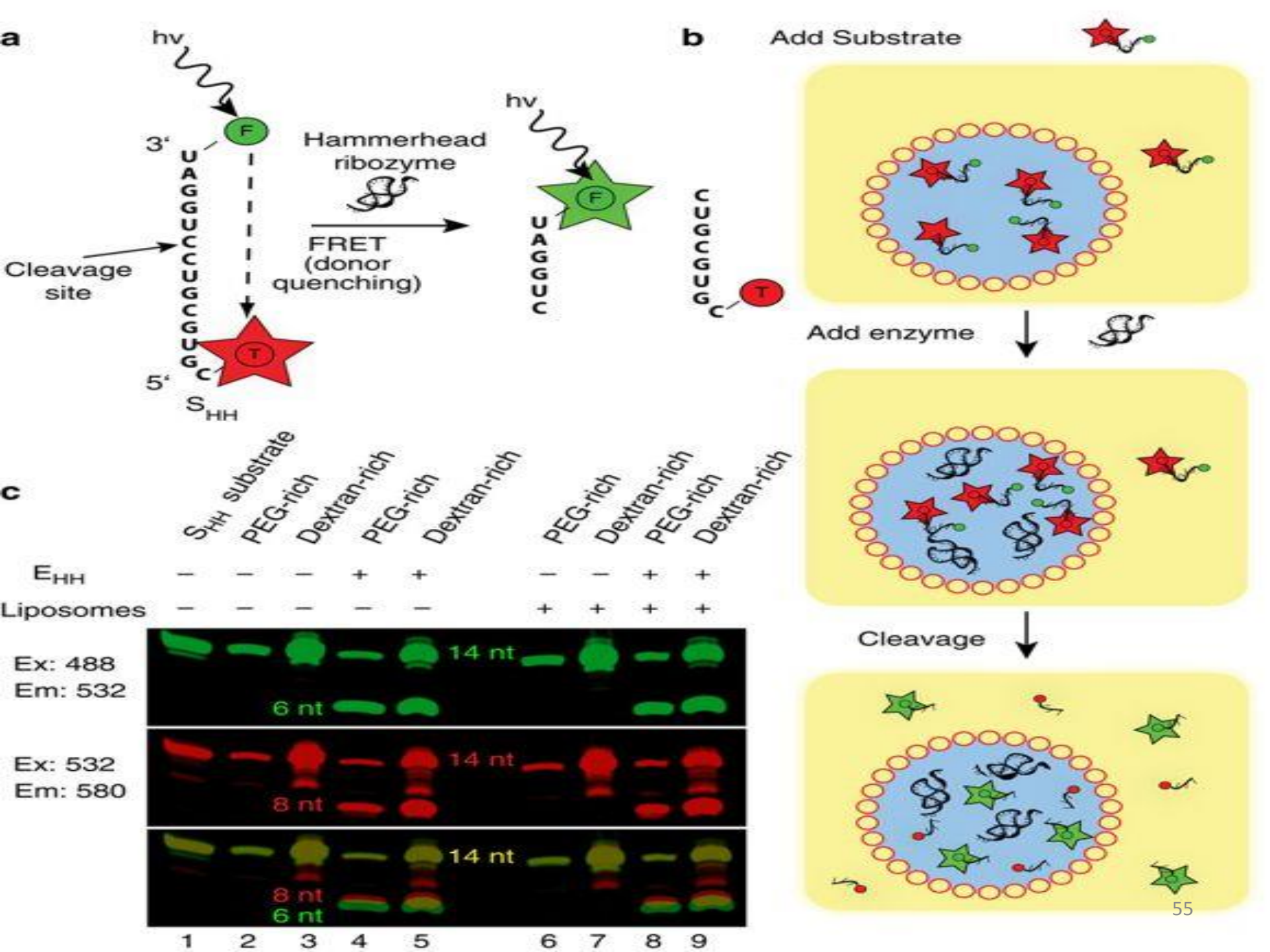
Mechanosensitive Liposomes as Artificial Chaperones for Shear-Driven Acceleration of Enzyme-Catalyzed Reaction Tomotaka Natsume and Makoto Yoshimoto*(2014)



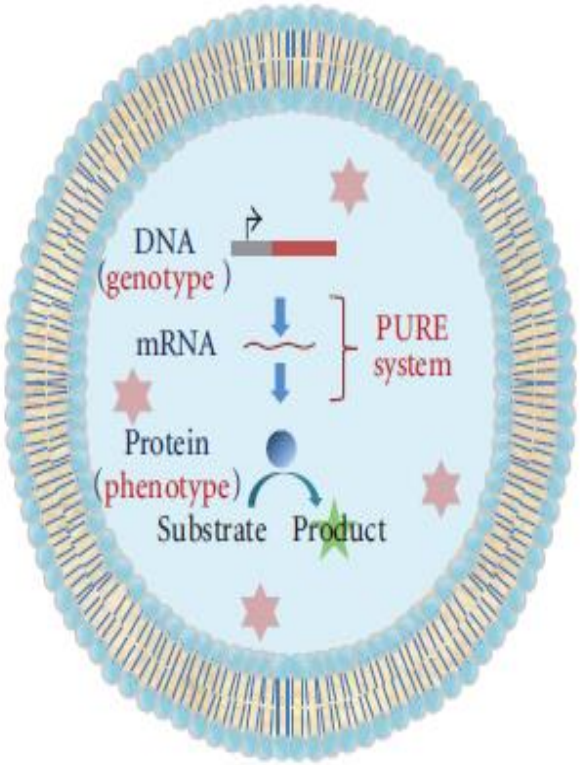


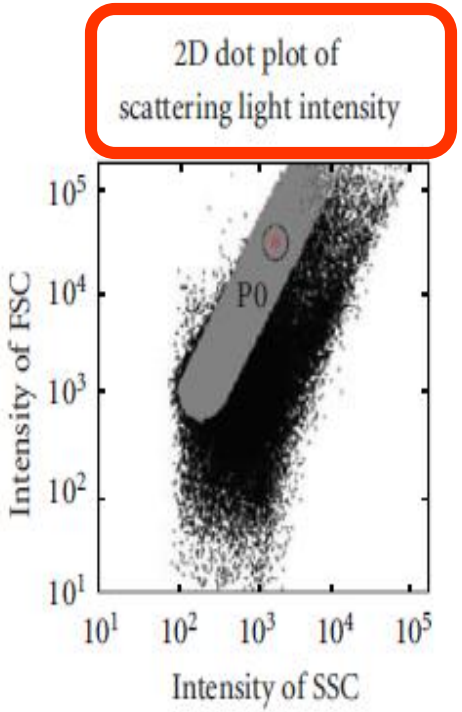


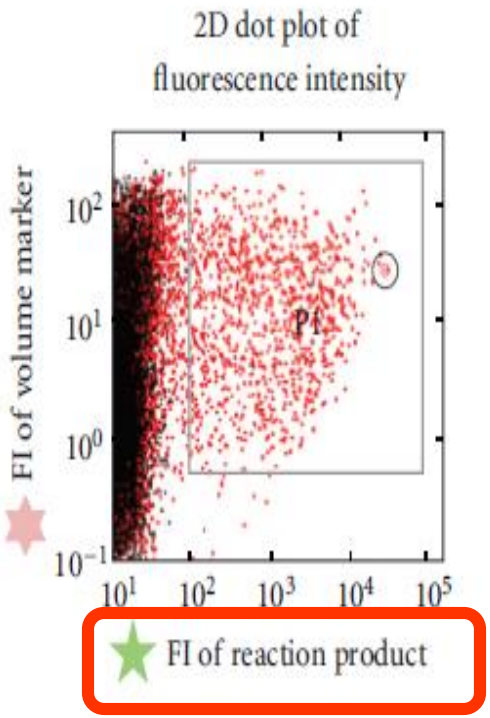
A liposome-actuated enzyme system and its capability as a self-biomineralized silica nanoreactor† S. Municoy and M. G. Bellino(2017) *


a
hv
3'
F
UAGGUCCUGGCGUGC
Hammerhead ribozyme
FRET (donor quenching)
Cleavage site
T
5'
S HH
hv
F
UAGGUC
CUGCGUG
C
T
b
Add Substrate
Add enzyme
Cleavage
c
S HH substrate
PEG-rich
Dextran-rich
PEG-rich
Dextran-rich
PEG-rich
Dextran-rich
PEG-rich
Dextran-rich
E HH
Liposomes
Ex: 488
Em: 532
14 nt
6 nt
Ex: 532
Em: 580
14 nt
8 nt
14 nt
8 nt
6 nt
1 2 3 4 5 6 7 8 9

Characterization of in-liposome **protein synthesis** using an **FACS** (37)







Volume marker

Reaction product

P0: Population of unilamellar liposomes

One of the data points corresponds to a liposome

P1: Population of unilamellar liposomes exhibiting catalytic activity

Liposomes Application as Drug Carrier

- Enzymes
- Anti Cancer Drugs
- Anti Fungal Drugs
- Anti Viral Drugs
- Anti Bacterial Drugs
- Anti parasite Drugs
- Different Types Of Nucleic Acid inTransgenesis
- AS Adjuant

(1)


Doxil®
DaunoXome®
Depocyt®
Mepact®
Marqibo®
Myocet®
Onivyde™
Abelcet®
Ambisome®
Amphotec®
Cancer therapy
Fungal diseases
Marketed liposomes
Viral vaccines
Analgesics
Photodynamic therapy
Epaxal®
Inflexal® V
DepoDur™
Exparel®
Visudyne®

Mode of action of liposomal-cell interactions[14]

I. **Lipases enzyme** degrades the liposomes membrane
II. **Fusion** with the plasma membrane of the target cells
III. A kind of receptor-mediated **endocytosis**

✓ **level of liposome–cell interaction is strongly :**

I. **nature of the charge**
II. **density of the charge**

Mode of action of liposomal drug interactions[14]

- **Nature** Of The Lipid Bilayer
- **Size** Of The **Drug** Molecules
- **Drug Interactions** With The Lipid Membrane
- **polarity** and partition coefficient

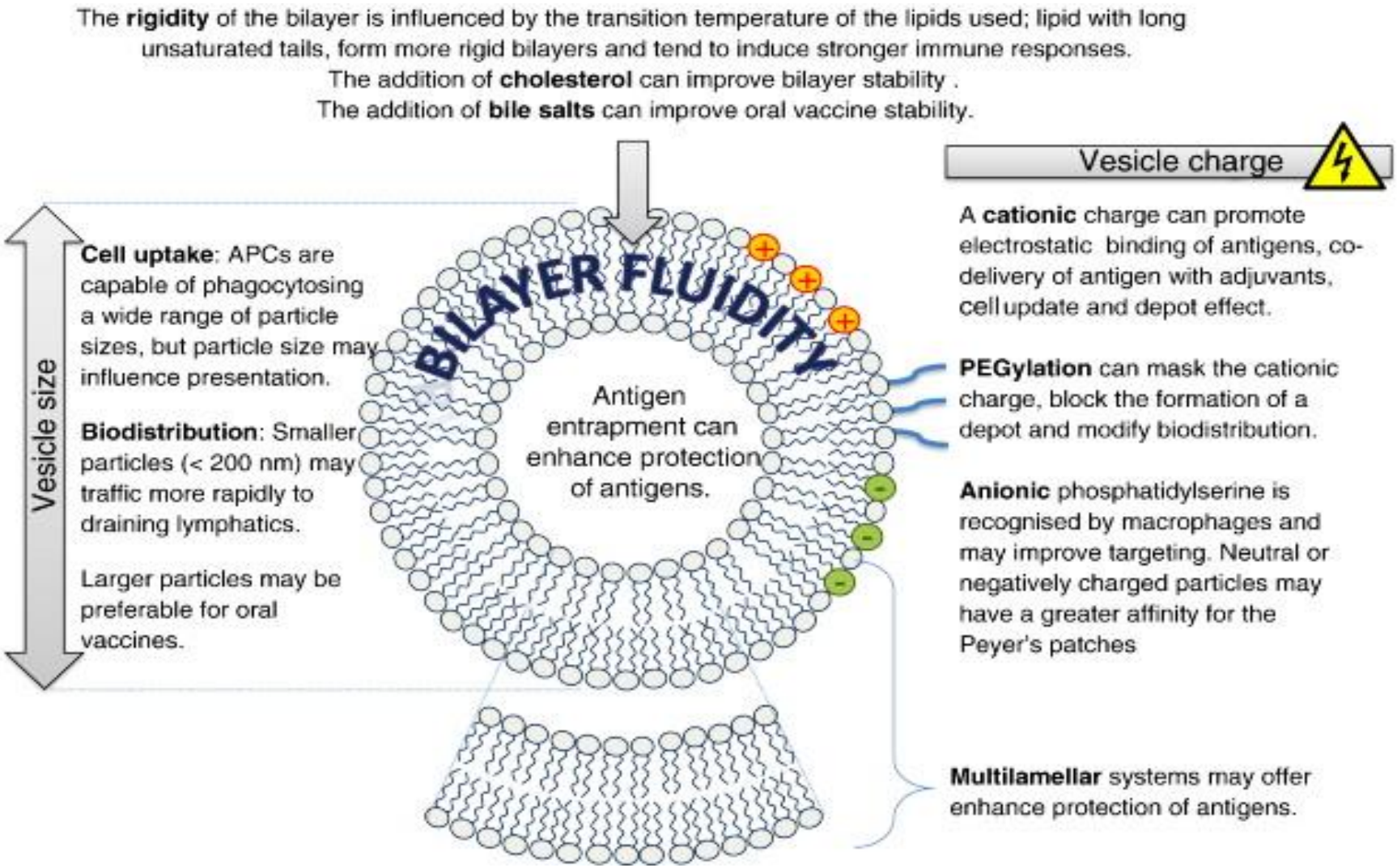
I. **Hydrophobic** drugs resides in the acyl hydro carbon chain of the liposome

II. **Polar** localize in the aqueous core (very close to the polar head groups)

The use of liposomes in veterinary vaccine formulations [33]
Liposome use in the delivery of drugs in the veterinary field

Encapsulated agent	Drug activity
Proteins or whole cell extracts	Antimicrobial
Plasmids encoding vaccine antigens	Antitumoral
Lipid	Immunosuppresor
Adjuvants and immunomodulators	Analgesic
	Anti-inflammatory
	Diagnostic imaging

AS vaccine adjuvants including bilayer rigidity , vesicle size vesicles , biodistribution , antigen location and vesicle charge [34]



FDA approved liposomal-based therapeutics[4]

Drug	Disease	Type Of Liposomal-based Delivery System
Verteporfin	Molecular Degeneration	Cationic
Vincristine	Non-hodgkin Lymphoma	Conventional
Amphotericin B	Anti-fungal Prophylaxis	Conventional
Cytarabine Or Cytosine Arabinoside	Neoplastic Meningitis And Lymphomatous Meningitis	Conventional
Morphine Sulfate	Pain Management	Conventional
Doxorubicin	Leukemia, Breast Cancer, Bone Cancer, Lung Cancer, Brain Cancer	Pegylated
Doxorubicin And Bortezomib	Relapsed Or Refractory Multiple Myeloma	Pegylated
Daunorubicin	Leukemia and solid tumors	Conventional

Phase I trial liposomal-based therapeutics[4]

Drug	Disease	Type Of Liposomal-based Delivery System
Sirna	Ovarian Cancer	DOPC Neutral Liposomes
Mitoxantrone LEM-ETU	Acute Myeloid Leukemia, Multiple Sclerosis, And Prostate Cancer	Cationic
Vinorelbine	Newly Diagnosed Or Relapsed Solid Tumors	Conventional
Thermosensitive Doxorubicin	Chest Wall Recurrences Of Breast Cancer	Pegylated
Irinotecan	Advanced Refractory Solid Tumors And Colorectal	Pegylated
Camptothecin Analog	Ovarian Cancer	Pegylated

Phase II trial liposomal-based therapeutics[4]

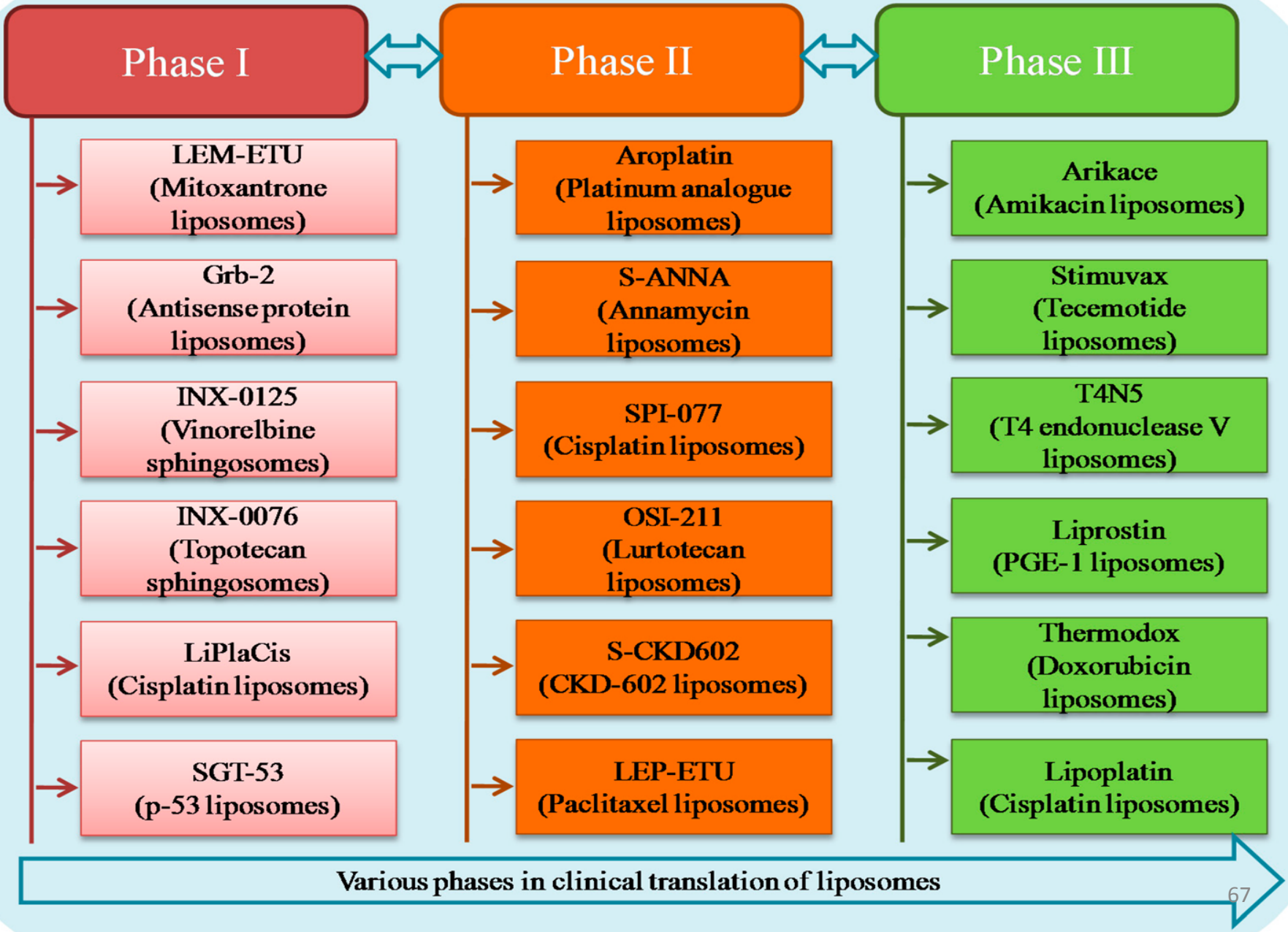
Drug	Disease	Type Of Liposomal-based Delivery System
Paclitaxel Endotag-1	Advanced Triple-negative Breast Cancer	Cationic
Paclitaxel Endotag-1	Pancreatic Cancer	Cationic
Tretinoin	Acute Promyelocytic Leukemia And Hormone-refractory Prostate Cancer	Conventional

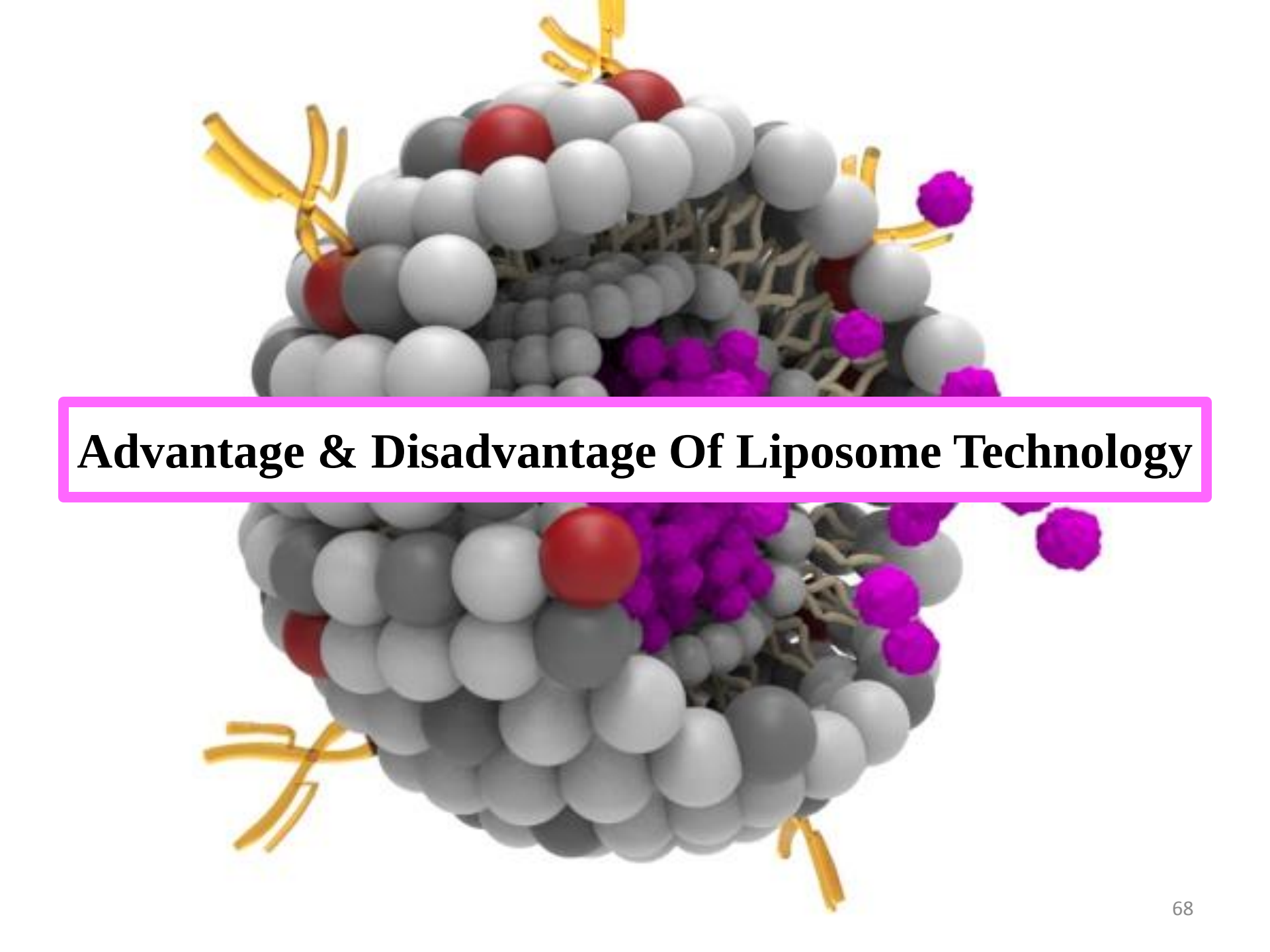
❖**Thermosensitive doxorubicin (Liver tumors) ,Phase III PEGylated**

Phase I/II trial liposomal-based therapeutics[4]

Drug	Disease	Type Of Liposomal-based Delivery System
Paclitaxel LEP-ETU	Advanced Triple-negative Breast Cancer	Sirna
Amikacin	Lung Infection	Conventional
Irinotecan SN-38 Cancer	Metastatic Colorectal	Conventional
Annamycin	Acute Lymphoblastic Leukemia	Conventiona
Lurtotecan	Ovarian Cancer, Head, And Neck Cancer	Conventional
Topotecan	Advanced Solid Tumors	Conventional
Nystatin	Fungal Infections	Conventional

Liposomes present under different phases of clinical trial investigation(1)





Advantage & Disadvantage Of Liposome Technology

Liposomal Porphyrinoid

- Porphyrin photosensitizers are mostly used components in photodynamic therapy (PDT). [23]
- liposomes as delivery for porphyrinoids overcome many drawbacks of conventional photosensitizers.[24]
- further development is necessary for metallo-porphyrin doped liposomes to become general delivery mechanisms[25]
- the liposomal structures for delivery of photosensitizers, a novel class of phototransducing liposomes called"porphysomes".[26]
- The delivery of photosensitizers to the tumor cells using liposome vehicles can help to overcome this problem. [23]

ADVANTAGES(30)

- **passive targeting** to tumor tissues.
- Site avoidance effect (**avoide non-target** tissues).
- Increased efficacy and therapeutic index.
- Reduces toxicity or **Non-toxic**.
- ability for **self-assembly**
- **Bio**degradable.
- **Non-imm**unogenic.
- Protection of **sensitive drug** molecules.
- **Enhance** drug solubilisation (Amphoterecin, Cyclosporins).
- Improved **pharmacokinetic** effects.

DISADVANTAGES

- Production cost is high .
- Batch to batch variation
- Leakage & fusion of encapsulated molecules.
- Some times phospholipids undergoes. oxidation & hydrolysis like reaction.
- Short half-life
- Low solubility

Advantages and Disadvantages[29]

Table 1. Advantages and Disadvantages of Injectable Delivery Systems

System	Advantages	Disadvantages
Polymeric devices	long-lasting drug concentrations less fluctuation in plasma concentrations increased compliance and QOL	poor release profile instability of formulation need for local anesthesia (implants)
Liposomes	improved pharmacokinetics ($\uparrow t_{1/2}$, $\uparrow$ AUC, $\downarrow C_{max}$, $\downarrow V_d$, $\downarrow$ Cl) decreased toxicity passive targeting	sequestration into RES vascular "leak" difficulty in achieving long-term physiochemical stability activation of complement
Pegylation	improved pharmacokinetics ($\uparrow t_{1/2}$, $\downarrow$ Cl, $\downarrow C_{max}$) less fluctuation in plasma concentrations enhanced in vivo activity decreased toxicity increased compliance and patient QOL decreased immunogenicity increased physiologic and chemical stability	loss of activity with improper selection of PEG and/or pegylation

Cl = plasma clearance; C_{max} = maximum plasma concentration; PEG = polyethylene glycol; QOL = quality of life; RES = reticuloendothelial system; $t_{1/2}$ = elimination half-life; V_d = volume of distribution.

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از توجه شما متشکرم